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14. ABSTRACT

The major goals and aims of this study are to investigate whether differences in cognitive outcome are related to mechanism of injury as well as white matter integrity using diffusion tensor imaging (DTI). We are also collecting and analyzing data in order to determine whether MR variables of interest are associated with psychosocial/clinical outcome, and whether there are group differences by mechanism of injury. Specifically, in the context of this study, we use novel, sophisticated MRI methods (e.g., quantitative diffusion tensor [DT] tractography) in order to characterize white matter changes seen within and across TBI subtypes, identify those at highest risk for poor outcomes, and gain knowledge about potential interventions to aid in recovery of brain functioning and cognition. In addition, we seek to identify the unique psychosocial challenges posed by differing mechanisms of injury as well as investigate the contribution of genetic factors (Apolipoprotein-E ε-4 [APOE ε4] and brain-derived neurotrophic factor [BDNF]) to brain integrity, neuropsychological functioning, and neurobehavioral outcome.

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INTRODUCTION

Aims and goals of the current project were to examine whether TBI history (mild to moderate blast and blunt force TBI) is associated with white matter changes using diffusion tensor imaging (DTI), and whether Veterans with history of head injury demonstrate differences in cognitive and psychosocial outcome. Primary aims use novel, sophisticated MRI methods (e.g., quantitative diffusion tensor [DT] tractography) in order to characterize white matter changes seen within and across TBI subtypes, identify those at highest risk for poor outcomes, and gain knowledge about potential interventions to aid in recovery of brain functioning and cognition. In addition, in our exploratory aim, we seek to identify the unique psychosocial challenges posed by differing mechanisms of injury as well as investigate the contribution of genetic factors (Apolipoprotein-E ε-4 [APOE ε4] and brain-derived neurotrophic factor [BDNF]) to brain integrity, neuropsychological functioning, and neurobehavioral outcome.

BODY

Growth and Expansion: As we near the end of this award that is currently in its third no-cost extension (NCE) year, we have many reportables to provide the DoD. We credit the DoD and this particular grant that was awarded 7 years ago to our strong productivity as well as, more generally, the overall success of our lab which continues to grow while our collaborations expand as well. In regards to the former, we now welcome an exceptionally talented postdoctoral fellow to our lab (Victoria Merritt; she will begin formally this Summer 2017), and we have added two key personnel (Kristina Lapira and Samreen Haque) who have come on board as research assistants. We have also submitted a multi-site grant to the DoD CDMRP, and I have an LOI under review that would represent the next important stage made possible by the original DoD grant discussed in detail here. The former is an intervention study while the latter is a combined DTI and arterial spin labeling (ASL) grant that would focus on a finding that we recently demonstrated: balance and dizziness represent commonly experienced postconcussive symptomatology (PCS), and we believe that white matter and blood flow changes interact to produce these troubling symptoms. Again, we are grateful to the DoD that has allowed us to conduct this important research since 2009, and we are hopeful that we will be in position to continue this work in our next phase of hopeful funding.

Productivity:
We continue to be productive in our work within our laboratory. Relevant to the aims and goals of the DoD award, this past year we presented 5 studies at the 44th Annual Meeting of the International Neuropsychological Society (Boston, MA, 2016). We are set to present another 5 studies at the 45th Annual INS meeting in February 2017. Over the past year, we have published 6 manuscripts, with an additional 2 recently accepted and in press. We currently have 5 relevant manuscripts in preparation (more detail can be found in the *Reportable Outcomes* section).

Recruitment:
During this 6th year of our DoD study, we have recruited and tested roughly 22 participants who represent either combat controls or patients who have sustained mild to moderate TBI; 11 participants partially completed the study (e.g., completing only cognitive testing or scanning) or were excluded due to failed drug screens on the day of testing (e.g., recent drug abuse). There are an additional 91 participants that were screened, but not included given that they did not meet inclusion criteria and were

thus excluded from participating). We have conducted approximately 638 phone screens of potential subjects throughout the course of the study. To date, we have enrolled a total of 142 subjects. Our recruitment rate is typically about 1-2 subjects per month. Our attrition rate is close to 0; our study subjects are informed in advance about the duration of the study, so they almost always complete both the cognitive assessment and neuroimaging sessions.

Due to challenges recruiting appropriate normal control participants and TBI participants who are blast-exposed only that meet our inclusion criteria, we requested and were approved for a third one-year NCE (approved 09/30/2016). In order to fulfill our SOW aims and to increase sample sizes (particularly with respect to rounding out our normal control and TBI blast-only samples to assist in group comparisons of the neuroimaging, neuropsychological, and other data) we have taken the following steps regarding recruitment: (1) we have recreated both our normal control and TBI-centered recruitment flyers to be more specific and easily understandable (2) we have focused our recruitment efforts on the VA TV advertisement, which, for each research study, displays the recruitment information for two weeks at time (due to the high number of studies, they rotate the advertisements for fairness) at this VASDHS location, as well as at other San Diego VA outpatient clinics; (3) we have also better utilized word-of-mouth referral with our current TBI and control participants by asking them to share our study information with Veteran friends who may qualify, emphasizing that a history of TBI is not necessary for participation; (4) we continue to share/obtain referrals through other similar VA research studies, and regularly receive new referrals from the VA TBI and Cognitive Rehabilitation Clinic. Although many participants end up being excluded for reasons such as substance abuse or metal shrapnel precluding MRI, this clinic has consistently served as an excellent source of new TBI Veteran referrals this past year; and (5) we have added two new undergraduate volunteer research assistants (mentioned above) to our team to focus primarily on recruitment efforts; they are currently receiving rigorous training with respect to phone recruitment, and are quickly learning the TBI literature and inclusion/exclusion criteria of this protocol.

KEY RESEARCH ACCOMPLISHMENTS

Total Sample Recruited Under DoD award to date:

Total recruited N=142 (TBI: n = 88; Controls: n = 54)

TBI Severity Breakdown:
87% Mild
11% Moderate
2% Severe

Average # of TBIs 2.55 (1.39)
Average # of Blast exposures 4.07 (13.76)

Most Significant TBI Types:
20% Blast
63% Blunt or Blast/Blunt

Statement of Work: Specific Aims and Work Accomplished

Specific Aim 1: To determine whether hippocampal atrophy and microstructural white matter changes can be detected in mild to moderate TBI and to assess differences by mechanism of injury (blast vs. blunt force).

***Hypothesis 1a*: Collapsed across group, TBI participants will demonstrate poorer fractional anisotropy (FA) in TBI predilection sites (i.e., anterior and posterior limbs of the internal capsule, genu and splenium of the corpus callosum, fornix) as well as lower hippocampal volumes than normal control (NC) participants.**

We have previously published results showing that TBI participants with reduced executive functions demonstrated significantly decreased fractional anisotropy (FA) of prefrontal white matter, corpus callosum, and cingulum bundle structures compared with both TBI participants without reduced executive functions and military control participants (Sorg et al., 2014). We later showed that history of TBI significantly predicted lower FA values in both the genu of the corpus callosum and in the left cingulum bundle; FA also negatively correlated with processing speed (Sorg et al., 2016). Interestingly, this more recent study showed that, while FA was negatively associated with processing speed, it was not associated with memory or PTSD symptom ratings.

We noted as the study progressed that a high number of individuals with TBI frequently fail effort, or performance validity, tests. We therefore set out to study this directly within our sample and recently published a report investigating the relationship between poor effort and white matter integrity in our sample. Interestingly, contrary to expectations, we found that mTBI veterans who failed performance validity tests demonstrated more overall white matter abnormalities than the other groups (i.e., those who passed effort testing); controls with no history of TBI). Regional white matter analyses revealed abnormalities in the anterior internal capsule and cingulum of both TBI subgroups relative to controls. Moreover, compared with the TBI-passed group, the TBI-failed group demonstrated significantly decreased white matter integrity in the corpus callosum.

We now have a manuscript in press (Clark et al., 2016a) showing that TBI participants with poor clinical outcome (cognitive fatigue complaints) show reduced white matter integrity in a striato-thalamocortical circuit (anterior internal capsule) known to mediate fatigue. These findings build upon those from existing functional neuroimaging studies in those with history of TBI, providing further evidence for the neural basis of cognitive fatigue in head injured adults.

More recently, we have been working to expand upon our imaging analyses to include additional ROIs that include long-coursing fibers (e.g., superior longitudinal fasciculus) that may be vulnerable to shear/tensile forces and other tracts critical for cognition (e.g., uncinate fasciculus may be important for executive functioning and/or memory). Analyses are currently underway.

***Hypothesis 1b*: Given suggestions in the literature that DTI may be more sensitive to TBI-related diffuse axonal injury, we expect that, across mechanism of injury, white matter integrity for all regions of interest will be more strongly associated with and predictive of TBI status than hippocampal volumes.**

As would be expected given the milder TBI severity of our sample, hippocampal volumes do not discriminate between groups (all p-values > .05). Instead, as hypothesized, we have found a number if differences between our TBI and control groups on white matter integrity as reflected by DTI (as described above).

***Hypothesis 1c*: Since individuals with blast injury frequently experience concomitant damage related to acceleration-deceleration and CNS compromise secondary to other internal injuries (e.g., lungs), it is expected that, when directly compared to the blunt TBI subgroup, the blast TBI subgroup will show lower FA values for each white matter tract of interest.**

We first explored whether those with blunt vs. blast TBI differed on right and left hippocampal volumes. Next we explored Freesurfer derived volumetric indices from the following cortical areas of the temporal lobe: superior, middle, and inferior temporal; banks of the superior temporal sulcus; fusiform; transverse temporal; entorhinal; temporal pole; parahippocampal. There were no significant differences between TBI subtypes (blast vs. blunt/blast) on any volumetric neuroimaging variables. Importantly, pure blast related injuries are unfortunately rare in our sample and thus power is quite limited. However, when we compare the small sample of individuals with pure blast TBI (n = 20) to those with pure blunt force trauma we see no significant differences in FA across any ROIs. In general, our sample was exposed to blast multiple times throughout deployment. While the vast majority of these injuries did not result in a TBI, subconcussive blast injuries may also be playing a part in white matter alterations and we continue to explore ways to further examine this.

<u>Specific Aim 2</u>: To investigate whether differences in cognitive outcome are related to mechanism of injury as well as to hippocampal volumes and white matter DTI variables.

***Hypothesis 2a*: We expect blast injury to be related to greater diffuse brain effects than blunt force injury. Thus, in comparison to the blunt force TBI subgroup, the blast TBI subgroup will show more pronounced cognitive deficits, particularly in executive functioning, attention/working memory, and processing speed.**

Preliminary analyses show no significant differences across the groups on any measure: Delis-Kaplan Executive Function System (D-KEFS) Color-Word Interference, Fluency, and Trails subtests; California Verbal Learning Test-2nd Edition; Wechsler Intelligence Scale for Adults 4th edition (WAIS-IV) Coding, Symbol Search, and Digit Span subtests; the Rey-Osterrieth Complex Figure Task; Reading subtest of the Wide Range Achievement Test- 4th edition (all *p*-values > .05). <u>However, a few comparisons were significant (or showed a trend towards significance), with blast showing worse performance than blunt force TBI. See below for values gleaned from independent samples t-tests:</u>

- WCST Perseverative Responses (p = .025)
- D-KEFS Category Fluency Animals (p = .062)
- WMS 4 VR Recognition (p = .084)
- CVLT Long Delay Free Recall (p = .061)
- CVLT Long Delay Cued Recall (p = .016)

Group Statistics

	Subject Type	N	Mean	Std. Deviation	Std. Error Mean
WCST perseverative responses raw	blast	19	10.16	6.627	1.520
	blunt	52	7.08	4.329	.600
DKEFS category fluency (animals) raw	blast	19	38.53	7.820	1.794
	blunt	55	42.89	8.890	1.199
WMS VR-IV recognition raw	blast	13	6.00	1.080	.300
	blunt	46	6.59	.717	.106
CVLT-II Long Delay Free Recall	blast	19	9.45	4.298	.986
	blunt	57	11.21	3.200	.424
CVLT-II Long Delay Cued Recall	blast	19	9.79	3.980	.913
	blunt	57	11.77	2.639	.350

**We plan to embark upon more in-depth analyses with the neurocognitive variables such as examining number of impaired scores in the battery, number of declined scores in the battery (i.e., number of scores that are significantly lower than estimated level of pre-morbid functioning), and neurocognitive performance variability*

Hypothesis 2b: Collapsed across group, hippocampal volumes will be positively associated with and predictive of memory performance in TBI. Additionally, in line with our preliminary DTI studies, we expect that anterior FA measures will be positively related with executive functioning and processing speed, whereas posterior FA measures will be positively associated with language and memory functions.

We examined whether hippocampal volume and temporal lobe variables were associated with cognition in the TBI group. Significant findings are listed below:

- Rey-O Percentile was significantly associated with right (r =-.353, p = .029) and left (r =-.369, p = .023) hippocampal volumes.
- Wechsler Memory Scale-IV recognition raw was significantly associated with right hippocampal volume (r = .332, p = .039). Better performance was associated with greater volume.
- Next, we created a memory composite variable and explored hippocampal volume associations. However, the memory composites did not appear to be as sensitive as examining individual tests of memory, as there were no significant correlations.

We are currently writing up findings relevant to this Aim that we presented at the International Neuropsychological Society conference (Denver, 2015) in which we investigated white matter DTI measures of frontothalamic structural connectivity (FTSC). We found that, although groups did not differ in measures of FTSC, FTSC was associated with mTBI severity. Additionally, within the mTBI group, right FTSC correlated with an executive function composite, while left FTSC correlated with higher levels of self-reported disinhibition and executive dysfunction.

Our plan is to continue data processing and explore whether history of TBI interacts with hippocampal

volume to predict memory test performance. However, when we test the interaction between TBI history and hippocampal volumes on cognition and control for PTSD we only find trending associations. Our plan is to follow up by increasing the sample size while also exploring the direct influence of PTSD. Additional alternative analytic avenues we plan to pursue include determining whether those with history of TBI who meet clinical criteria for PTSD differ from those who not meet criteria for this psychiatric disorder.

Specific Aim 3: To determine whether MR variables of interest are associated with psychosocial/clinical outcome and whether there are group differences by mechanism of injury.

***Hypothesis 3a*: Given greater sensitivity to microstructural damage, FA of white matter in anterior regions will be more strongly associated with psychosocial clinical outcome than hippocampal volumes across TBI subgroups. Thus, in comparison to NC participants, lower FA of anterior regions will be associated with greater levels of psychological distress (i.e., depression, anxiety, and post-traumatic stress related symptomatology) and poorer functional outcomes.**

Throughout the period of this award, we have repeatedly showed that anterior white matter is indeed a predilection site for TBI, which is consistent with several other studies in the literature. More recently, we demonstrated that TBI significantly predicted FA values in both the genu of the corpus callosum and in the left cingulum bundle; FA also negatively correlated with processing speed (Sorg et al., 2016). Additionally, while FA was negatively associated with processing speed, it was not associated with memory or PTSD symptom ratings.

Given that white matter in the *cerebrum* did not show tight associations with psychosocial outcome as hypothesized, we investigated white matter integrity in the brainstem and then examined associations with commonly experienced postconcussive symptomatology (e.g., vestibular symptoms such as dizziness and imbalance). Historically, DTI studies of the brainstem have been considerably limited given challenges specific to being able to properly and accurately image this region (small, densely packed fibers with bony artifact). In a study published within a special journal series (Delano-Wood et al., 2015), we found that FA of the corticospinal tract was significantly negatively associated with LOC duration in participants with TBI history in our sample. In addition, lower FA of certain tracts – most especially the pontine tegmentum – was significantly associated with increased PCS symptoms (i.e., vestibular symptoms) and poorer physical functioning, even after adjusting for PTSD symptoms. Trends were also observed between lower pontine tegmentum FA, bodily pain, and greater fatigue. Lower FA of corticospinal tract and medial leminscus was significantly associated with poorer emotional well-being after adjusting for PTSD symptoms.

More recently, we published a brief report showing Clark et al. (2016a) that white matter disruptions of the left anterior internal capsule is significantly associated with greater levels of cognitive fatigue in Veterans with history of mild-to-moderate TBI.

In addition, to exploring direct relationships between MR variables and psychosocial/clinical outcome, we also sought to characterize how those with history of TBI may differ from MCs.

-Schiehser et al. (2015; manuscript) examined the relationship between postconcussive symptoms and quality of life (QOL) in Veterans with mild TBI. Results showed that perceived QOL was significantly worse in Veterans with mild-moderate TBI than in controls. In the TBI group, QOL was predominantly associated with affective symptoms, and moderate to strong correlations with fatigue and depression were evident across all QOL areas. Multivariate analyses revealed depression and fatigue to be the best predictors of Psychological, Social, and Environmental QOL, whereas sleep difficulty best predicted Physical QOL in mild-moderate TBI. Veterans with post–acute mild-moderate TBI evidence worse QOL than demographically matched Veteran controls. Affective symptoms, and specifically those of fatigue, depression, and sleep difficulty, appear to be the most relevant postconcussive symptoms predicting QOL in this population.

-Kim et al. (2016; abstract) found that when examining the relationship between subjective complaints of neurobehavioral symptoms and executive dysfunction/disinhibition, mood, and objective performance on an Go/No-Go inhibition task in mTBI veterans, self-reported executive dysfunction/disinhibition and depression were negatively associated with task performance. Further analyses demonstrated that higher levels of self-reported depression was the only significant predictor of task performance over and beyond the effects of subjective cognitive complaints or PTSD symptomatology. These results indicate depression as a potential treatment target for neurobehavioral symptoms related to disinhibition in mTBI veterans.

-Hanson et al. (2016; manuscript) characterized alcohol use among mTBI veterans and examined its relationship to mTBI and psychiatric symptoms. The mTBI group reported more alcohol-related psychosocial problems (e.g., fights, poor judgment, physical injuries, emotional problems) relative to MCs ($p<.03$). Within mTBI, more lifetime alcohol-related psychosocial problems were associated with combat exposure, longer post-traumatic amnesia from blunt injury, and higher depression, anxiety, and PTSD symptoms, as well as neurobehavioral symptoms ($ps<.05$). Additionally, greater lifetime withdrawal symptoms were associated with poorer attention and visual learning ($ps<.03$), while recent alcohol-related psychosocial problems were associated with poorer executive functioning ($ps<.03$). Our findings suggest that lifetime alcohol-related psychosocial or withdrawal symptoms may affect post-concussive symptomatology and cognitive functioning in some veterans with a history of mTBI.

Hypothesis 3b: **Since blast injury may be associated with greater psychological trauma secondary to exposure to improvised explosive devices—as well as the higher prevalence of other orthopedic injuries—it is posited that, after controlling for injury severity, individuals with blast TBI will show greater levels of psychological distress (i.e., depression, anxiety, and post traumatic related symptomatology) and poorer functional outcomes (i.e., greater deficits in work status and quality of life) than blunt force TBI.**

Although those with TBI consistently show significantly greater levels of depression, PTSD, anxiety and substance use when compared to military controls, to date we have found no differences by blast and blunt force injury. We will continue to recruit "pure blast" participants who have experienced mild to moderate head injury and will investigate subscores within the scales we examined (Beck Anxiety Inventory, Beck Depression Scale, PCL-M, Modified Cognitive Fatigue Scale; WHO-QOL).

We are currently finalizing a manuscript that examines the associations between employment,

satisfactory social support, and cognitive functioning among Veterans with mild to moderate TBI (Moore et al.). We found that employment and stronger levels of social support, which are important for positive health outcomes, are associated with better global cognition, particularly within the domains of attention and processing speed and language. Analyses show no differences by mechanism of injury, however. Future studies are needed in order to explore whether engagement in pro-social activities over time provides a buffering role against cognitive decline in Veterans in the aftermath of head injury.

<u>Genetic Exploratory Aim</u>: Since genetic and neurotrophic factors have been implicated as being possibly involved in both risk for and recovery from complications secondary to TBI, an exploratory aim is of the current study is to investigate two of these factors (apolipoprotein-ε4 [APOE-ε4] and brain-derived neurotrophic factor [BDNF]) as they relate to brain integrity, cognition functioning, and clinical/behavioral outcome. It has been suggested that APOE ε4 may be associated with decreased transport of lipids, increased accumulation of beta-amyloid, increased brain inflammation, impaired brain perfusion after injury, and poorer repair.[56-59] Indeed, a recent meta-analysis showed that the presence of the APOE ε4 allele is associated with increased risk of poor long-term outcome at 6 months after injury,[60] and it has also been shown to be related to duration of post-traumatic coma,[61] poorer neurorehabilitation outcome post TBI,[62] impaired cognitive performance in relation non-ε4 positive patients with TBI,[63] and slower recovery rate than those without the ε4 allele over a two-year period.[64] However, effects of the APOE ε4 allele are controversial as some studies have not shown any associations with neurological or cognitive outcome in TBI.[65-67] Much less is known about the effect of BDNF as a possible neuroprotective factor in the context of TBI. BDNF is a critical regulator of activity-dependent synaptic plasticity,[68,69] and it has been shown to be involved in neuronal survival and growth.[70] It has also been associated with improving cognitive and neurological deficits due to ischemia.[71] To our knowledge, however, no study has investigated BDNF in mild to moderate neurotrauma, and studies investigating relationships between BDNF and white matter, cognition, and clinical outcome are needed in the literature. Thus, we plan to investigate both APOE ε4 and BDNF in our sample of patients with TBI in order to better understand contributions of these genetic factors to white matter integrity and neurobehavioral outcome in blast and blunt-force TBI. We expect that, consistent with histopathological findings in the literature, participants with the APOE ε4 allele will demonstrate poorer white matter integrity and cognitive/clinical outcome even after controlling for age, time since injury, and severity of injury. Additionally, we expect that higher levels of BDNF will be associated with higher white matter integrity in predilection sites as well as better cognitive and clinical long-term outcomes (adjusting for age, time since injury, and injury severity). It is hoped that data obtained will be used as pilot data for future grant applications to explore associations between APOE, BDNF and longer-term outcome in our sample.

Genotyping has been complete on 64 TBI and 38 Military Control subjects. With respect to BDNF, we have completed two studies (published abstracts) that focus on (1) cognitive outcome and (2) brain structure associations. The first which stems from a presentation we gave at INS last year (2016) is currently being finalized and prepared for journal submission. The second is being prepared for presentation next month in New Orleans. A manuscript should be generated the May 2017.

(1) Brain-Derived Neurotrophic Factor (BDNF) Genotype is Related to Executive Function in Veterans with History of Mild Traumatic Brain Injury

Nicole D. Evangelista, Alexandra L. Clark, Madeleine L. Werhane, Scott F. Sorg, Dawn M. Schiehser, Russell Kim, Mark W. Bondi, Katherine J. Bangen, & Lisa Delano-Wood

Objective: Brain-derived neurotrophic factor (BDNF) plays a role in neurogenesis and synaptic plasticity of hippocampal and forebrain areas; however, its expression is largely influenced by genotype. Compared with individuals without a BDNF Met allele, research shows Met-allele carriers have abnormal BDNF secretion. However, whether BDNF genotype is related to cognitive outcome, and how any association is modified by history of traumatic brain injury (TBI), is unclear. We therefore sought to clarify the relationship between BDNF genotype and cognition in Veterans with and without a history of mild TBI (mTBI). **Participants and Methods**: 117 Veterans (mTBI=72, Military Controls [MCs]=45]) underwent BDNF genotyping and were divided into (1) Met+ (n = 34 mTBI; n = 12 MCs), and (2) Met- (n = 41 mTBI; n = 33 MCs) carrier groups. Participants completed psychiatric symptom inventories and were administered neuropsychological tests that were reflected as the following composite scores in analyses: memory (CVLT: Total Learning, and Short and Long Delay Free Recall) and executive function (DKEFS: Verbal Fluency Switching Total Switching, Trails Number-Letter Sequencing; and WCST Perseverative Responses). **Results:** ANCOVA, controlling for psychiatric symptoms, revealed a significant Group x Genotype interaction for the executive function composite (p = .01). Examination of simple main effects revealed TBI+/Met- carriers performed significantly worse than TBI+/Met+ carriers, but no such association was found across genotype in the MC group. No significant interaction was observed for memory performance. **Discussion:** Results show that BDNF genotype is associated with poorer executive functioning but not memory performance in our sample of Veterans with mTBI. Though the underlying mechanism remains poorly understood, Met- carriers may be especially vulnerable to executive dysfunction after neurotrauma. Future studies are needed to further explore the epigenetic implications of BDNF on cognitive outcome in the context of head injury.

(2) Brain Derived Neurotropic Factor (BDNF) Val66Met Moderates the Association Between PTSD and Cortical Thickness in Veterans with History of Traumatic Brain Injury

Nicole D. Evangelista, Alexandra L. Clark, Katherine J. Bangen, Scott F. Sorg, Madeline L.Werhane, Dawn M. Schiehser, & Lisa Delano-Wood

Objective: Post-traumatic stress disorder (PTSD) has been linked to cortical thinning of frontal and temporal regions in Veterans with history of traumatic brain injury (TBI). However, it remains unclear how brain-derived neurotrophic factor (BDNF)—a protein that plays a role in neuronal growth, maturation and maintenance—may potentially influence the effects of PTSD on the brain. We therefore sought to clarify the associations between BDNF genotype, PTSD, and cortical thickness in Veterans with history of mild TBI (mTBI). **Participants and Methods:** 59 Veterans with history of mTBI underwent BDNF genotyping and were divided into (1) Met+ carrier (n=29) and (2) Met- carrier (n=30) subgroups. Participants also completed psychiatric symptom questionnaires (PCL-M) and structural MR imaging. Cortical thickness values were derived from parcellated regions of interest (ROIs) using FreeSurfer. **Results:** Analysis of covariance controlling for age, revealed a significant PTSD x Genotype interaction for cortical thickness in the cuneus, precuneus, and the rostral anterior cingulate (p's <0.05). Examination of simple main effects revealed that Met+ carriers with greater PTSD symptomology demonstrated significantly thinner cortices relative to Met- carriers (p's < .05). **Conclusions:** Results

show that BDNF genotype differentially affects the relationship between PTSD and cortical thickness in Veterans with history of mTBI. Specifically, mTBI Met+ carriers—who may have lower levels of this critical neurotrophin available in the central nervous system— appear to be especially vulnerable to the negative effects of PTSD on cortical thickness of several brain regions. These findings suggest that BDNF genotype plays an important role in modulating brain structure in the context of comorbid TBI and PTSD. Future studies should further evaluate the epigenetic effects of BDNF on recovery and treatment outcomes in Veterans with comorbid TBI and PTSD.

Work focused on APOE-e4 genotype

Historically, we have had some difficulty with low numbers of APOE-e4's in our TBI group (the genotype is overrepresented in our control group). We have very recently begun to analyze data toward our first manuscript focused on APOE

DTI Variables of Interest: Per the Aims and Hypotheses of the award, we examined 10 white matter ROIs within the TBI group but found no significant differences across APOE-e4 allele groups. However we do find a trend for the left anterior internal capsule which shows reduced FA and higher MD in the APOE-e4+ group ($p = .051$)

Neurocognitive Variables: To date, we still have difficulty in showing significant differences across APOE groups. However, a few comparisons have been shown to be significant (or showed a trend towards significance), with e4+ participants demonstrating *worse* performance than e4- participants:

- WAIS 4 Coding ($p = .017$)
- D-KEFS Color-Word Inhibition ($p = .076$)
- WMS 4 LM II ($p = .049$)
- WMS 4 LM Recognition ($p = .060$)
- WMS 4 VR Recognition ($p = .077$)
- CVLT Trials 1-5 Total Recall ($p = .061$)
- IGT Total ($p = .078$)

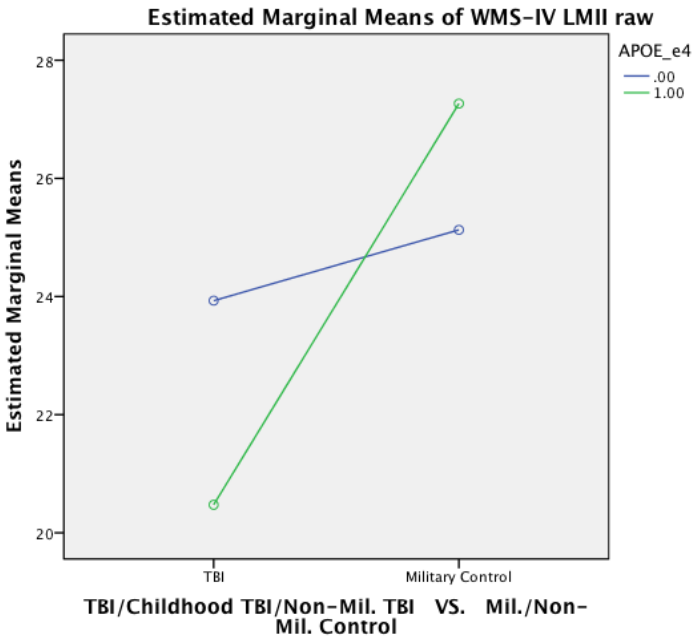
We are currently conducting more in-depth analyses such as examining number of impaired scores in the battery, number of declined scores in the battery (i.e., number of scores that are significantly lower than estimated level of pre-morbid functioning), and neurocognitive performance variability

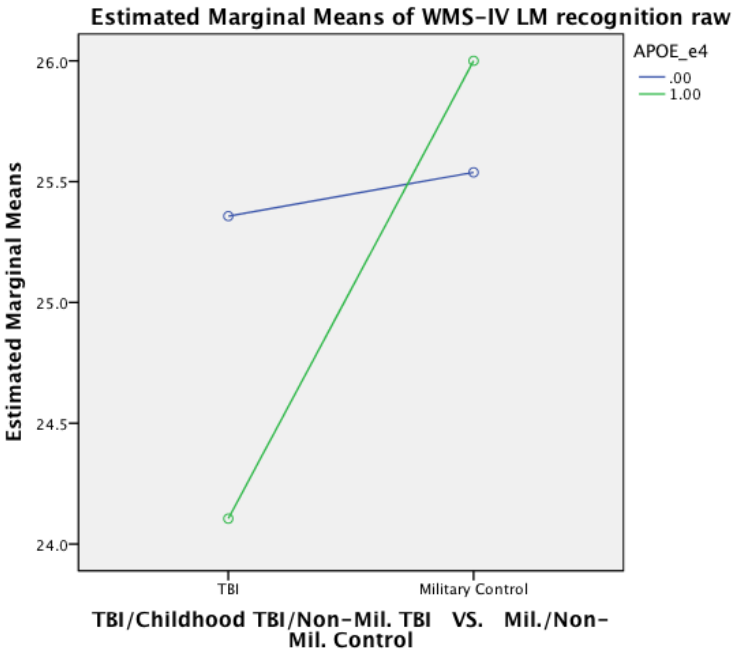
Behavioral/Psychosocial Variables: Interestingly, we found several significant differences found between e4+ and e4- participants on neuropsychiatric status variables, with e4+ participants showing greater symptoms than e4- participants across the following measures:

- BDI Total Score ($p = .029$)
- BAI Total Score ($p = .028$)
- PCL Total Score ($p = .036$)
- NSI Total Score ($p = .075$)
- MFIS Total Score ($p = .051$)
- Additionally, APOE- ε4 status was significantly associated with poorer physical functioning (SF-36 Physical Functioning, $p = .037$) and greater role limitations due to physical disability (SF-36 Role Physical subscale, $p = .028$).

We are now examining the symptom clusters associated with each questionnaire in order to get a better sense of what might be contributing to the group differences. Additionally, we plan to examine symptom inventory summary indices (investigate subscales) which should better inform how groups differ.

Below are representative plots showing differences between APOE groups (e4+ and e4-) on both memory recall and recognition performance. We show interactions such that presence of the e4 allele appears to be protective in controls but deleterious in those with TBI. Given that we find these types of relationships frequently across our cognitive battery, we are currently working to refine our analyses for our first manuscript focused on APOE analyses.





REPORTABLE OUTCOMES

Relevant Manuscripts Published or In Press in 2016:

Published in 2016:

1. Clark, A.L., Delano-Wood, L., Sorg, S.F., Werhane, M.L., Hanson, K.L., & Schiehser, D.M. (2016a). Cognitive Fatigue is Associated with Reduced Anterior Internal Capsule Integrity in Veterans with History of Mild to Moderate Traumatic Brain Injury. *Brain Imaging and Behavior [epub ahed of print]*.

2. Clark, A.L., Sorg, S.F., Schiehser, D.M., Luc, N., Bondi, M.W., Sanderson, M., Werhane, M.L., & Delano-Wood, L. (2016b). Deep White Matter Hyperintensities Affect Verbal Memory Independent of PTSD Symptoms in Veterans with Mild Traumatic Brain Injury. *Brain Injury, 30*(7), *864-871*.

3. Hanson, K. L., Schiehser, D. M., Clark, A. L., Sorg, S. F., Kim, R.T., Jacobson, M.W., Werhane, M.L., Jak, A.J., Twamley, E.W., & Delano-Wood, L. (2016). Problem Alcohol Use in Veterans with Mild Traumatic Brain Injury: Associations with Cognitive Performance and Psychiatric Symptoms. *Journal of Clinical & Experimental Neuropsychology [epub ahed of print]*.

4. Clark, A.L., Sorg, S.F., Schiehser, D.M., Bigler, E., Bondi, M.W., Jacobson, M.W., Jak, A.J., & Delano-Wood, L. (2016c). White Matter Associations with Performance Validity Testing in Veterans with Mild Traumatic Brain Injury: The Utility of Biomarkers in Complicated Assessment. *Journal of Head Trauma Rehabilitation, 31*(5), *346-59*.

5. Sorg, S. F., Schiehser, D. M., Bondi, M. W., Luc, N., Clark, A. L., Jacobson, M.W., & Delano-Wood, L. (2016). White Matter Microstructural Compromise Is Associated With Cognition But Not

Posttraumatic Stress Disorder Symptoms in Military Veterans With Traumatic Brain Injury. *The Journal* of *Head Trauma Rehabilitation, 31*(5), *297-308.*

6. Bomyea, J., Lang, A.J., Delano-Wood, L., Jak, A.J., Hanson, K.L., Sorg, S.F., Clark, A.L., & Schiehser, D.M. (2016). Neuropsychiatric Predictors of Post-Injury Headache After Mild-Moderate Traumatic Brain Injury in Veterans. *Headache, 56*(4), *699-710.*

***Manuscripts In Press**:*

1. Clark, A.L., Bangen, K.J., Sorg, S.F., Schiehser, D.M., Evangelista, N.D., McKenna, B., Liu, T.T., & Delano-Wood., L. (In Press). Dynamic Relationship Between Perfusion and White Matter Integrity Across Time Since Injury in Veterans with History of TBI. *NeuroImage: Clinical.*

2. Werhane, M.L., Evangelista, N.D., Clark, A.L., Sorg, S.F., Bangen, K.J., Schiehser, D.M., Tran, M., & Delano-Wood, L. (In Press). Pathological Vascular and Inflammatory Biomarkers of Acute and Chronic Phase Traumatic Brain Injury: Review. *Concussion.*

Manuscripts Under Review:

Moore, R.C., Fazeli, P.L., Zlatar, Z.Z., Clark, A.L., Delano-Wood, L., Eyler, L.T., & Schiehser, D.M. (Under Review). Preliminary evidence for an association between employment, satisfactory social support, and cognitive functioning among veterans with mild to moderate traumatic brain injury. *Journal of Clinical and Experimental Neuropsychology*.

Manuscripts In Preparation:

1. Evangelista, N.D., Clark, A.L., Werhane, M.L., Sorg, S.F., Schiehser, D.M., Kim, R.T., Bondi, M.W., Bangen, K.J., & Delano-Wood, L. (In Preparation). Brain-Derived Neurotrophic Factor (BDNF) Genotype is Related to Executive Function But Not Memory Performance in Veterans with History of Mild Traumatic Brain Injury.

2. Sorg, S.F., Clark, A.L., Schiehser, D.M., Bondi, M.W., & Delano-Wood, L. (In preparation). Brain Derived Neurotrophic Factor (BDNF) Genotypes Moderate the Relationship between PTSD symptoms and Cortical Thickness in Veterans with Mild TBI.

3. Sorg, S.F., Clark, A.L., Schiehser, D.M., Bondi, M.W., Jak, A.J., Hanson, K.L., Woods, S.P., & Delano-Wood, L. (In Preparation). Intra-Individual Variability in Tests of Executive Functions in Veterans with Mild TBI: Associations with White Matter Microstructure.

4. Sorg, S.F., Luc, N., Clark, A.L., Kim, R.T., Bondi, M.W., Schiehser, D.M., & Delano-Wood, L. (In preparation). Frontothalamic Structural Connectivity in Veterans with Mild Traumatic Brain Injury: Associations with Executive Functions.

5. Merritt, V., Werhane, M., Clark, A.C., Sorg, S.F., Schiehser, D.M., & Delano-Wood, L. (In preparation). APOE-e4 Genotype Modifies Cognitive Outcome in Veterans with History of Mild to Moderate TBI.

The following published abstracts were completed and presented in 2016 with joint funding from the DoD and VA:

1. Evangelista, N.D., Clark, A.L., Werhane, M.L., Sorg, S.F., Schiehser, D.M., Kim, R.T., Bondi, M.W., Bangen, K.J., & Delano-Wood, L. (2016, February). *Brain-Derived Neurotrophic Factor (BDNF) Genotype is Related to Executive Function But Not Memory Performance in Veterans with History of Mild Traumatic Brain Injury*. Poster presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA.

2. Clark, A.L. Bangen, K.J., Sorg, S.F., Luc, N., Schiehser, D.M., Sanderson, M., Werhane, M.L., Bondi, M.W., & Delano-Wood, L. (2016, February). Links Between Perfusion, White Matter Integrity, and Cognition in Veterans with History of Mild-to-Moderate TBI. Paper presented orally at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA.

3. Moore, R.C., Delano-Wood, L., Kim, R.T., Hanson, K.L., Sorg, S.F., Clark, A.L., Zlatar, Z.Z., Fazeli, P.L., Eyler, L.T., & Schiehser, D.M. (2016, February). *Engagement in an Active Lifestyle is Associated with Better Neurocognitive Functioning Among Veterans with Mild Traumatic Brain Injury*. Poster presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA.

4. Karen L. Hanson, Dawn M. Schiehser, Elizabeth Twamley, Amy J. Jak, Alexandra L. Clark, James B. Lohr, Dean C. Delis, & Lisa Delano-Wood (2016, February). Alcohol Misuse is Associated with Increased Psychiatric Symptomatology and Reduced Processing Speed in Veterans with Mild Traumatic Brain Injury. Poster presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA.

CONCLUSION

We have made considerable progress toward our stated goals as outlined in our Introduction above. Given greater collaborations with other VA TBI investigators, our laboratory has grown considerably and productivity has increased significantly. We expect to be especially productive this final year, especially in regard to increased recruitment efforts, as we continue to grow our lab while also rounding out our data collection so that we can then embark upon large-scale studies to test many of the hypotheses set forth in the original proposal

REFERENCES

PDFs of Published Manuscripts from 2016:

1. Clark, A.L., Delano-Wood, L., Sorg, S.F., Werhane, M.L., Hanson, K.L., & Schiehser, D.M. (2016). Cognitive Fatigue is Associated with Reduced Anterior Internal Capsule Integrity in Veterans with History of Mild to Moderate Traumatic Brain Injury. *Brain Imaging and Behavior [epub ahed of print]*.

2. Sorg, S. F., Schiehser, D. M., Bondi, M. W., Luc, N., Clark, A. L., Jacobson, M.W., & Delano-Wood, L. (2016). White Matter Microstructural Compromise Is Associated With Cognition But Not

Posttraumatic Stress Disorder Symptoms in Military Veterans With Traumatic Brain Injury. *The Journal* of *Head Trauma Rehabilitation, 31*(5), *297-308.*

3. Clark, A.L., Sorg, S.F., Schiehser, D.M., Luc, N., Bondi, M.W., Sanderson, M., Werhane, M.L., & Delano-Wood, L. (2016). Deep White Matter Hyperintensities Affect Verbal Memory Independent of PTSD Symptoms in Veterans with Mild Traumatic Brain Injury. *Brain Injury, 30*(7), *864-871*.

4. Hanson, K. L., Schiehser, D. M., Clark, A. L., Sorg, S. F., Kim, R.T., Jacobson, M.W., Werhane, M.L., Jak, A.J., Twamley, E.W., & Delano-Wood, L. (2016). Problem Alcohol Use in Veterans with Mild Traumatic Brain Injury: Associations with Cognitive Performance and Psychiatric Symptoms. *Journal of Clinical & Experimental Neuropsychology [epub ahed of print]*.
Hanson…

5. Clark, A.L., Sorg, S.F., Schiehser, D.M., Bigler, E., Bondi, M.W., Jacobson, M.W., Jak, A.J., & Delano-Wood, L. (2016). White Matter Associations with Performance Validity Testing in Veterans with Mild Traumatic Brain Injury: The Utility of Biomarkers in Complicated Assessment. *Journal of Head Trauma Rehabilitation, 31*(5), *346-59*.

6. Werhane, M.L., Evangelista, N.D., Clark, A.L., Sorg, S.F., Bangen, K.J., Schiehser, D.M., Tran, M., & Delano-Wood, L. (In Press). Pathological Vascular and Inflammatory Biomarkers of Acute and Chronic Phase Traumatic Brain Injury: Review. *Concussion*.

7. Bomyea, J., Lang, A.J., Delano-Wood, L., Jak, A.J., Hanson, K.L., Sorg, S.F., Clark, A.L., & Schiehser, D.M. (2016). Neuropsychiatric Predictors of Post-Injury Headache After Mild-Moderate Traumatic Brain Injury in Veterans. *Headache, 56*(4), *699-710.*

8. Clark, A.L., Bangen, K.J., Sorg, S.F., Schiehser, D.M., Evangelista, N.D., McKenna, B., Liu, T.T., & Delano-Wood., L. (In Press). Dynamic Relationship Between Perfusion and White Matter Integrity Across Time Since Injury in Veterans with History of TBI. *NeuroImage: Clinical*.

APPENDICES

Published manuscripts mentioned in References are attached.

Brain Imaging and Behavior
DOI 10.1007/s11682-016-9594-6

BRIEF COMMUNICATION

Cognitive fatigue is associated with reduced anterior internal capsule integrity in veterans with history of mild to moderate traumatic brain injury

Alexandra L. Clark[1,2] · **Lisa Delano-Wood**[2,3,4] · **Scott F. Sorg**[2,4] · **Madeleine L. Werhane**[1,2] · **Karen L. Hanson**[2,4] · **Dawn M. Schiehser**[2,3,4]

Abstract No known studies have directly examined white matter microstructural correlates of cognitive fatigue post-TBI in a Veteran sample. We therefore investigated the relationship between cognitive fatigue and white matter integrity in Veterans with history of mild to moderate TBI (mmTBI). 59 Veterans (TBI = 34, Veteran Controls [VCs] = 25]) with and without history of mmTBI underwent structural 3T DTI scans and completed questionnaires related to cognitive fatigue and psychiatric symptoms. Tractography was employed on six regions of interest, including the anterior and posterior limbs of the internal capsule; genu; body and splenium of the corpus callosum; and cingulum bundle. Group analyses revealed that those with history of mmTBI displayed significantly greater levels of cognitive fatigue relative to those with no history of head injury (p = .02). Within the mmTBI group, independent of psychiatric symptoms, decreased white matter microstructural integrity of the left anterior internal capsule was associated with greater levels of cognitive fatigue (p = .01). Results show that the subjective experience of cognitive fatigue following neurotrauma may be linked to the disruption of striato-thalamo-cortical tracts that are important in mediating arousal and higher-order cognitive processes. These findings build upon those from existing functional neuroimaging studies in those with history of TBI, providing further evidence for the neural basis of cognitive fatigue in head injured adults.

Keywords Fatigue · Cognitive fatigue · White matter microstructure · TBI

Introduction

Cognitive fatigue—or the inability to initiate and sustain cognitive tasks and activities—is a common and often chronic symptom following traumatic brain injury (TBI) (Bushnik et al. 2008; Ponsford et al. 2012). Estimates suggest that 58–67 % of individuals with history of TBI relative to 18–30 % of non-injured controls endorse significant levels of cognitive fatigue (Ouellet and Morin 2006; Schiehser et al. 2016), and the negative impact of fatigue on well-being and quality of life has been well documented (Cantor et al. 2008; Schiehser et al. 2015a). Accordingly, cognitive fatigue has been linked to greater levels of depression and anxiety, slower recovery, and increased rates of disability across various levels of TBI severity (Bay and de-Leon 2011; DeLuca 2005; Ponsford et al. 2011). However, despite its prevalence and profoundly negative influence on functional outcome, the overall nature and underlying neural basis of cognitive fatigue in TBI has yet to be systematically evaluated.

While research exploring the neural basis of cognitive fatigue following TBI is limited, studies of cognitive fatigue in other clinical populations (e.g., multiple sclerosis, Parkinson's disease) suggest that cognitive fatigue may result from disruption of the non-motor functions of the basal ganglia (Chaudhuri and Behan 2000; Dobryakova et al. 2013). Importantly, the basal ganglia nuclei play a critical role in

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motivation and reward behavior and, although the exact mechanism remains poorly understood, cognitive fatigue may be the result of an imbalance in the perception of effort-reward valuations (Boksem and Tops 2008; Chaudhuri and Behan 2000; Dobryakova et al. 2013). This imbalance may result from central nervous system damage, as cognitive fatigue has been linked to metabolic, structural, and functional brain alterations in the striatal-thalamic-frontal cortical system (see Cantor et al. 2013; Dobryakova et al. 2013 for review). Within the context of TBI, the white matter pathways critically involved in this network and adjacent areas may be particularly vulnerable to neurotrauma since acceleration/deceleration and rotational forces—either by blunt-force trauma or blast-related injury—contribute to stretching and shearing of cerebral white matter (Chatelin et al. 2011). These primary areas of cellular deformation may lead to diffuse disruption and possible disconnection of white matter pathways (Povlishock and Katz 2005). Given that no known studies have examined the potential link between white matter and subjective experience of cognitive fatigue in Veterans post-TBI this exploratory study sought to clarify any potential link between fatigue and diffusion tensor imaging (DTI) indices of tracts known to be vulnerable to neurotrauma in Veterans with history of mild to moderate TBI (mmTBI).

Methods

Study participants were 59 (TBI: n = 34, VCs: n = 25) Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn (OEF/OIF/OND) Veterans recruited directly from posted recruitment flyers and TBI outpatient clinic referrals within the VA San Diego Healthcare System (VASDHS). All study participants provided written and informed consent and subsequently underwent neuropsychological testing and magnetic resonance imaging (MRI) scanning at the University of California, San Diego (UCSD) Center for Functional MRI.

Exclusion criteria were as follows: (1) severe TBI (loss of consciousness [LOC] ≥ 24 h, alteration of consciousness [AOC] > 24 h, or posttraumatic amnesia [PTA] ≥ 7 days); (2) prior history of neurological conditions (e.g., epilepsy, multiple sclerosis) and/or serious medical illness (e.g., myocardial infarction, stroke); (3) current (within 30 days) substance or alcohol abuse as determined by the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition)-criteria (American Psychiatric Association 2000); (4) current or past history of bipolar disorder, schizophrenia, psychotic disorder, or active suicidal ideation; (5) any contraindications that would exclude MRI and; (6) any detection of 10 illicit drugs measured by the Rapid Response 10-drug Test Panel during prior to testing or MRI scanning.

TBI diagnostic procedure

All TBI participants reported a head-injury within the last 15 years, endorsed LOC, and met Department of Defense (DoD)/Department of Veterans Affairs criteria for mild or moderate TBI (2009). 71 % (n = 24) of the TBI participants met criteria for mild TBI (LOC < 30 min, and AOC or PTA < 24 h), while 29 % (n = 10) of the TBI participants met criteria for moderate TBI (LOC >30 min but <24 h, and AOC > 24 h or PTA >1 day but <7 days).

Cognitive subscale of the modified fatigue impact scale

Recently validated in mmTBI, the Modified Fatigue Impact Scale (MFIS) is a 21-item scale self-report measure that delineates fatigue into *physical* and *cognitive* subscales (Schiehser et al. 2015b). Given the scope and aims of the current investigation, only the *cognitive* subscale was examined, which consists of 10 items that may be summed to a total of 40. Items on the cognitive subscale are ranked on a likert scale and include: "I have difficulty paying attention for long periods of time" and "I have been unable to think clearly." Previously established cut-off criteria for the cognitive subscale also allowed for mmTBI individuals to be classified as "fatigued" (i.e., scores ≥18.5).

Symptom rating scales

Both VCs and TBI participants completed psychiatric symptom rating scales that included the PTSD Checklist ([PCL-M]; Weathers et al. 1993) and Beck-Depression Inventory-II ([BDI-II]; Beck et al. 1996). Given that several items on the BDI-II overlap with the measurement and characterization of fatigue, we utilized the affective subscale derived from the factor analysis of Siegert et al. (2009) as our measure of mood.

Neuroimaging protocols, processing, and analysis

All participants underwent structural MRI and diffusion tensor imaging (DTI) on a 3-Tesla General Electric MRI scanner using the MR750 platform. Structural Scanning: A sagitally acquired high-resolution 3D T1-weighted anatomical MRI was collected with the following parameters: FOV = 24 cm, 256 × 256 × 192 matrix, .94 x .94 × 1 mm voxels, 176 slices, TR = 20 ms, TE 4.8 ms., flip angle 12°, scan time: 7 min. Diffusion Tensor Imaging: DTI images were collected via dual spin echo EPI acquisition (Reese et al. 2003) with the following parameters: FOV = 240 mm, slice thickness = 3 mm, matrix size 128 X 128, in-plane resolution =1.875 X 1.875, TR 8000 ms, TE 93 ms, scan time: 12 to 16 min. Thirty-four slices were acquired with 61 diffusion directions distributed on the surface of a sphere in conjunction with the electrostatic repulsion model (Jones et al. 1999) and a b value of 1500 s/

mm^2. Collection also included one T2 weighted image with no diffusion (b = 0). Distortions due to a lack of magnetic field homogeneity were reduced via field map corrections.

Image processing The Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL) was used for DTI image preprocessing (Smith et al. 2004). FSL was used for motion correction and removal of non-brain voxels, and all images were visually inspected for quality control and assurance purposes. Fractional anisotropy (FA) was derived from FSL after voxel-by-voxel calculation of the diffusion eigenvalues.

Tractography After DTI preprocessing, TrackVis (Wang et al. 2007) was used to create the tracts of interest using fiber assignment by continuous tracking methods (Mori et al. 1999). White matter fiber tracts were generated from seeds placed via Wakana et al. (2004) procedures in nine regions of interest that included: left and right anterior and posterior limbs of the internal capsule; genu, body and splenium of the corpus callosum; and left and right cingulum bundle. These white matter tracts were chosen given their demonstrated vulnerability to neurotrauma (see Edlow & Wu, 2012) coupled with links to fatigue across other clinical populations (Bester et al. 2013; Hanken et al. 2015; Genova et al. 2013).

Each subject's color-coded map, seen by loading the principle eigenvector image in FSL, was generated to display each voxel's main orientation of diffusion. Seed placement occurred in the axial plane within green-colored voxels between the putamen and caudate for the anterior internal capsule, and within blue-colored voxels medial to the lenticular nucleus and lateral to the thalamus for the posterior internal capsule. For the cingulum bundle, seed placement occurred in the coronal plane within green-colored voxels inferior to the cingulum gyrus and superior to the corpus callosum. Seed placement for the corpus callosum occurred within red-colored voxels in a mid-saggital slice; the genu, body, and splenium subdivisions were identified using Concha and colleagues procedures (2005). Irregular tracking as restricted by the implementation of a 41-degree angle threshold and partial volume effects were reduced by inclusion of fractional anisotropy (FA) values greater than .20 (Mori and van Zijl 2002). Finally, FA was averaged over all voxels within a tract and utilized in subsequent analyses.

Statistical analyses

Group comparisons for continuous demographic and clinical data were conducted using Analysis of Variance. Chi-squared analyses compared groups in terms of categorical variables. Analysis of Covariance (ANCOVA) was used to compare the groups on cognitive fatigue. Bivariate Pearson's correlations were utilized to assess relationships between indices reflecting white matter integrity and cognitive fatigue. All DTI and fatigue correlations were Bonferonni corrected for multiple comparisons (α [.05/9] = .006). Multiple linear regressions were used to examine white matter integrity and fatigue associations within the context of psychiatric symptoms. All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 21 (SPSS IBM, New York, USA).

Results

Participant demographics and TBI injury characteristics are presented in Table 1. There were significant differences between the groups on ethnicity (p = .001), in that the mmTBI group had a higher proportion of Hispanics and Asians relative to the VC group. Moreover, the mmTBI group displayed more severe psychiatric symptomatology (p < .001) compared to the VC group, as well as experienced more than one head injury, were blast-exposed, and many months removed from initial injury during time of assessment.

VCs vs. mmTBI fatigue comparisons

ANCOVAs, controlling for psychiatric scores (i.e., BDI-II affective and PCL-M total score), revealed that the groups significantly differed in the severity of cognitive fatigue (F (55) = 5.84, p = .019, η = .096). The mmTBI group displayed more frequent problems with cognitive fatigue (*Mean* = 21.91, *SD* = 11.57) relative to the VCs group (*Mean* = 6.60, *SD* = 8.24). The groups significantly (p > .001) differed when cut-off criteria (i.e., fatigued vs. non-fatigued) was applied to the sample, with 76.5 % (n = 26) of individuals in the mmTBI group versus 12 % (n = 3) of the VCs group meeting cut-off criteria for significant cognitive fatigue. Given the relatively restricted range in combination with the few individuals who met criteria for fatigue in the VCs group, all subsequent analyses were restricted to the mmTBI group.

Fatigue and white matter associations

In an effort to understand whether cognitive fatigue was associated with white matter microstructural integrity, a series of bivariate correlations were first performed. After Bonferonni corrections (α = .006), a significant association between FA of the left anterior internal capsule (r = −.476, p = .004) and cognitive fatigue was revealed, such that worse white matter integrity was associated with greater levels of cognitive fatigue. See Fig. 1. No other significant associations between WM tracts (i.e., posterior internal capsule; genu, body splenium of corpus callosum; cingulum bundle) and cognitive fatigue were observed (all p's > .09).

A multiple linear regression analysis was performed to determine if the association between FA of the left anterior internal capsule and cognitive fatigue was independent of psychiatric

Table 1 Participant characteristics, mean (SD)

	mmTBI (n = 34)	VCs (n = 25)	F or χ^2	p
Age	33.06 (5.88)	33.48 (8.18)	.05	.82
Education	14.50 (1.50)	14.96 (1.90)	1.08	.30
WRAT-4 reading standard score	105.00 (10.70)	105.36 (7.57)	.02	.89
Gender (Male)	88 %	72 %	2.48	.15
Ethnicity				
Caucasian	38 %	84 %	19.58*	.001
African-American	6 %	4 %		
Hispanic	38 %	8 %		
Asian	18 %	0 %		
Native American	0 %	4 %		
BDI-II total score	21.49 (13.68)	5.32 (8.89)	26.60	< .001
BDI-II affective subscale score	9.97 (7.81)	2.48 (5.32)	17.10	< .001
PCL-M total score	46.68 (19.60)	21.72 (9.22)	34.76	< .001
Total number TBIs	3.06 (1.72)			
Months since most recent TBI	63.50 (34.27)			
Most significant TBI				
Blunt	68 %			
Blast	9 %			
Blast w/ blunt	23 %			
Blast exposed				
Yes	59 %			
No	41 %			

mmTBI mild-to-moderate TBI, *VCs* Veteran Controls, *WRAT-4* Wide Range Achievement Test-4th Edition, *BDI-II* Beck Depression Inventory II, *PCL-M* PTSD Checklist Military Version,
*Likelihood Ratio Utilized

symptoms. In the model, FA of the left anterior internal capsule and total scores for the BDI Affective and PCL-M total score were entered as predictors. Results revealed the overall model was significant F (3,33) = 13.49 p < .001 and explained 57.4 % of the variance in cognitive fatigue. Independent of depressive (β = .50, p = .009) and post-traumatic (β = .14, p = .44) symptoms, white matter microstructure of the left anterior internal capsule (β = −.32, p = .01) was significantly associated with cognitive fatigue. Results did not differ when TBI severity was included in a secondary set of analyses and in fact, severity (mild vs. moderate) of injury was not a significant predictor of cognitive fatigue (β = .03, p = .79) in the model.

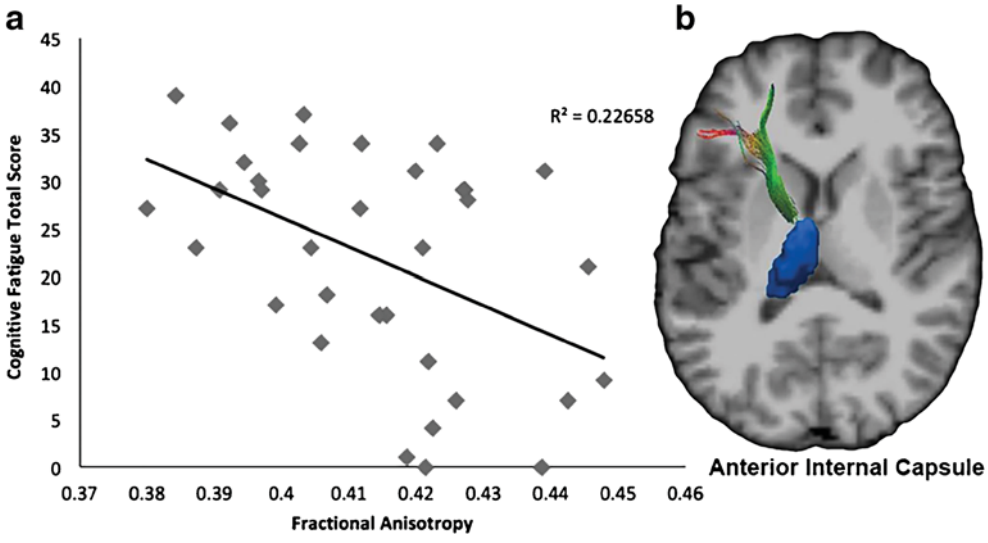

Fig. 1 White matter and cognitive fatigue. **a** Association between FA of left anterior internal capsule and cognitive fatigue. **b** Depiction of the left anterior internal capsule in green with thalamus as a reference point in blue

Discussion

Our study revealed that greater levels of cognitive fatigue were endorsed by those with history of mmTBI and furthermore, integrity of a fiber tract (internal capsule) critically involved in the basal ganglia circuitry was associated with greater levels of cognitive fatigue in those with history of mmTBI. Importantly, the anterior internal capsule runs from the thalamus to the frontal lobe, and connects (1) the lenticular and caudate nuclei and (2), frontal cortex with the corpus striatum. Structural damage to these white matter projections may lead to inefficient processing and/or regulation of arousal and awareness necessary for execution and completion of complex cognitive tasks (Bonelli and Cummings 2007; Dobryakova et al. 2013; Haber and Knutson 2010). This inefficiency may in turn manifest as greater subjective experience of fatigue in individuals with white matter damage. Indeed, a recent study of fatigue in individuals with multiple sclerosis also revealed that decreased white matter microstructural integrity of the anterior internal capsule was also associated with greater levels of self-reported fatigue (Genova et al. 2013).

While studies examining the relationship between structural neuroimaging findings and self-reported fatigue remains fairly limited in TBI, one functional MRI study revealed robust differences between *objective*, or task-based measures of fatigue, and fronto-striatal activity in those with history of head trauma relative to healthy controls (Kohl et al. 2009). Despite comparable levels of task accuracy between the groups, healthy controls showed decreased striatal activity during task performance over time, while those with history of TBI demonstrated sustained striatal activity and increased recruitment of the prefrontal cortex. Taken together, these results suggest increased recruitment and task-based activity is required for the same level of performance in those with history of TBI. In combination with these data, our results suggest that cerebral damage secondary to mmTBI may result in less neural efficiency, which could represent the underlying neural substrates of behaviorally manifested cognitive fatigue.

Although psychiatric symptoms have been associated with both white matter and fatigue in other samples (Kasai et al. 2008; Ponsford et al. 2015), our findings show that observed relationships between white matter and fatigue were independent of psychiatric symptoms. The relationship between fatigue and psychiatric symptoms is complex, and directionality is poorly understood (Bushnik et al. 2008; Cantor et al. 2008). Our results affirm that, within the context of mmTBI, psychiatric symptoms alone do not explain increased levels of cognitive fatigue or the relationship between cognitive fatigue and white matter integrity. In other words, the high rates of post-traumatic fatigue observed in TBI samples may be better explained by *neurotrauma-related* structural alterations as opposed to psychiatric comorbidities.

To our knowledge, the current study represents the first to examine the relationship between subjective cognitive fatigue and white matter integrity in a sample of Veterans with history of mmTBI. Strengths of the study include a well-characterized cohort of Veterans with mmTBI and use of a 61-direction DTI sequence to assess white matter integrity. However, there are some weaknesses of this study that should be noted. First, our VC group was smaller than the mmTBI group and had a relatively restricted range of cognitive fatigue scores, which may have made it difficult for us to detect DTI and fatigue associations. However, additional exploratory analyses revealed there were no significant FA and cognitive fatigue associations across any of the ROIs (all p's > .18) in the VC group. Future studies that take play in non-head injured or neurological samples that endorse clinically significant levels of cognitive fatigue may help to clarify any potential white matter and cognitive associations. Second, although a common limitation in TBI research, our diagnosis of TBI relied heavily on on restropective self-report and may be subject to recall bias. Finally, while isotropic voxel dimensions are optimal when performing tractography, the diffusion imaging data used in the current study consisted of non-isotropic voxel dimensions (Oouchi et al. 2007; Vos et al. 2011). This may have influenced estimation of FA and the total number of fibers generated during tractography (Liu et al. 2010; Oouchi et al. 2007). However, this limitation did not appear to carry a great impact on the results as the tracts generated from this data where highly consistent with the known neuroanatomy of the white matter pathways we sought to identify (e.g., the anterior internal capsule).

Taken together, results of the current study demonstrated that, independent of psychiatric symptoms commonly experienced in the context of head injury, white matter integrity of a critical striato-thalamo-cortico tract (left anterior internal capsule) was significantly associated with subjective reports of cognitive fatigue in Veterans with history of mmTBI. Disruption of this tract aligns well with purported models of fatigue, yet additional studies are needed—perhaps integrating both DTI and functional MRI—to further examine the complex interplay between fatigue, brain structure and function within the context of TBI.

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Compliance with ethical standards All procedures involved in this study were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975. Informed consent was obtained from all patients included in the study. Alexandra Clark, Lisa Delano-Wood, Scott Sorg, Madeleine Werhane, Karen Hanson, and Dawn Schiehser declare no conflicts of interest.

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White Matter Microstructural Compromise Is Associated With Cognition But Not Posttraumatic Stress Disorder Symptoms in Military Veterans With Traumatic Brain Injury

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Objective: To investigate white matter microstructure compromise in Veterans with a history of traumatic brain injury (TBI) and its possible contribution to posttraumatic stress disorder (PTSD) symptomatology and neuropsychological functioning via diffusion tensor imaging. **Participants and Methods:** Thirty-eight Veterans with mild ($n = 33$) and moderate ($n = 5$) TBI and 17 military control participants without TBI completed neuropsychological testing and psychiatric screening and underwent magnetic resonance imaging an average of 4 years following their TBI event(s). Fractional anisotropy (FA) and diffusivity measures were extracted from 9 white matter tracts. **Results:** Compared with military control participants, TBI participants reported higher levels of PTSD symptoms and performed worse on measures of memory and psychomotor-processing speed. Traumatic brain injury was associated with lower FA in the genu of the corpus callosum and left cingulum bundle. Fractional anisotropy negatively correlated with processing speed and/or executive functions in 7 of the 8 tracts. Regional FA did not correlate with memory or PTSD symptom ratings. **Conclusion:** Results suggest that current PTSD symptoms are independent of TBI-related white matter alterations, as measured by diffusion tensor imaging. In addition, white matter microstructural compromise may contribute to reduced processing speed in our sample of participants with history of neurotrauma. Findings of the current study add insight into the factors associated with complicated recovery from mild to moderate TBI. **Key words:** *diffusion tensor imaging*, *mild traumatic brain injury*, *neuropsychology*, *posttraumatic stress disorder*

TRAUMATIC BRAIN INJURY (TBI) and posttraumatic stress disorder (PTSD) are highly comorbid in Veterans of the recent conflicts in Iraq and Afghanistan.[1] Veterans with histories of TBI endorse higher rates of PTSD symptoms than those with other

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injuries,[1] and deployment-related TBI has been shown to predict the onset or exacerbation of PTSD symptoms, even beyond other contributing factors such as combat intensity.[2,3] In addition, the presentation of PTSD symptoms is reportedly of greater intensity in Veterans with histories of TBI than in those without reported neurotrauma.[4] Such findings echo those of civilian TBI studies that show heightened psychiatric distress following a TBI,[5] and they suggest that disruptions in brain function as a consequence of a TBI event may contribute to the manifestation of PTSD symptoms in Veterans.[6]

In samples without history of TBI, PTSD symptoms have been associated with structural alterations within cortical and subcortical regions within the frontal and temporal lobes including prefrontal cortices[7] the anterior cingulate,[8] the temporal cortex,[9] the hippocampus, and the amygdala.[10–12] Such findings support the theory that disrupted frontosubcortical circuitry in systems that mediate emotional regulation may contribute to the manifestation of PTSD symptoms.[13] Thus, damage within the white matter tracts interconnecting those frontal and limbic brain regions may also contribute to or exacerbate PTSD symptoms following a traumatic event. Although available studies linking white matter microstructure and PTSD symptoms have been limited, PTSD has been associated with microstructural damage within the cingulum bundle, a white matter tract connecting limbic regions (eg, cingulate cortex and hippocampus).[14,15] Posttraumatic stress disorder has also been tied to altered frontal white matter microstructure in frontal lobe regions (eg, prefrontal cortex; precentral gyrus) and in the internal capsule.[15] An examination of white matter pathways that may impact PTSD is particularly relevant in the context of TBI, as many of these same brain regions (ie, the prefrontal cortex) are consistently shown to be susceptible to TBI effects[16,17]—with brain white matter being particularly vulnerable to TBI even in its mild forms.[18–20]

The pathophysiological processes contributing to white matter compromise in mild TBI (mTBI) are complex. Generally, tensile forces upon white matter fibers at the initial time of the injury are thought to initiate damage that provokes a secondary cascade of neurochemical and neurotoxic processes responsible for the diffuse axonal injury often observed in TBI.[21] Traditional structural magnetic resonance imaging (MRI) techniques are not sensitive to the presence of mild forms of axonal injury due to the relative homogeneity of the T1 signal within white matter. Researchers have turned to diffusion tensor imaging (DTI), an MRI modality that is sensitive to the movement of water molecules within brain structures. In highly organized tissue, such as neural white matter, these patterns of molecular water movement can be used to describe the neuronal integrity of the tissue, a common index of which is fractional anisotropy (FA).[22] Fractional anisotropy values range from 0, in voxels where the diffusion is equal in all directions, to 1, in regions with a high degree of directional uniformity. Thus, higher FA values are indicative of healthy tissue with uniform structure, while relatively lower values suggest a disruption of this structure and tissue damage.[22] Reductions in FA may result from a decrease in axial diffusivity (AD) (diffusion along the principal diffusion direction [along the axon]), an increase in radial diffusivity (RD) (diffusion perpendicular to the primary diffusion direction), or an additive or synergistic effect of the 2. Although there is some debate as to the specific meaning of the component diffusion measures,[23,24] AD has most commonly been interpreted as describing axonal integrity, and RD has been described as a proxy for myelin integrity.[25] Many DTI studies have found evidence for disrupted white matter microstructure in frontal and limbic white matter regions in both mild and severe TBI non-Veteran populations.[26–34] A growing number of studies of Veterans with histories of mTBI have shown evidence of white matter abnormalities as well,[35–37] although such an effect is not always found.[38]

The purpose of this study was to investigate whether TBI-related damage to white matter tracts contributes to PTSD symptom severity and concomitant reduced cognitive performance. Tracts selected for analysis included specific pathways previously shown to be related to PTSD symptoms (eg, cingulum bundle and internal capsule) and those that interconnect frontal regions also implicated in PTSD (ie, genu and body divisions of the corpus callosum [CC]). We hypothesized that (1) a positive history of TBI would be associated with compromised microstructure in white matter pathways, including tracts that connect structures involved in emotional regulation (eg, cingulum bundle) and (2) greater disruption of the white matter would be associated with poorer cognitive performance and increased current PTSD symptom severity in a well-characterized sample of military Veterans with history of mild to moderate TBI.

METHODS

Participants

Data for this project were gathered from ongoing studies of TBI in returning Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) Veterans being conducted at the VA San Diego Healthcare System (VASDHS), with institutional review board approval from the VASDHS and the University of California, San Diego. Traumatic brain injury participants were recruited from outpatient TBI treatment clinics, from study advertisements within the VASDHS, and word of mouth. Forty-nine Veterans with reported TBI histories

were originally screened for participation in this study. Following application of exclusionary criteria, including exclusion of those with effort test results below published cutpoints,[39,40] a final sample of 38 Veterans with TBI participated. Another age-matched control group of OEF/OIF veterans with no reported history of TBI ($n = 17$) was also recruited for participation via study advertisements within the VASDHS and word of mouth.

TBI group inclusion/exclusion criteria

Operation Enduring Freedom/Operation Iraqi Freedom veterans diagnosed with a mild or moderate closed head TBI ($n = 38$) from either blast exposure (ie, secondary to Improvised Explosive Device, land mine, or rocket grenade) or mechanical force (ie, motor vehicle accident or other closed head injury [blunt trauma]) were included in the study. The criteria defined by the Department of Defense and Department of Veterans Affairs Traumatic Brain Injury Task Force were used for classifying injury severity in TBI.[41] Specifically, mTBI ($n = 33$) was defined as alteration of consciousness (AOC) or loss of consciousness (LOC) of 30 minutes or less; if available, an initial Glasgow Coma Scale[42] score between 13 and 15; a posttraumatic amnesia (PTA) of 24 hours or less; and no visible lesions on magnetic resonance image or computed tomographic scan. Moderate TBI ($n = 5$) was defined as LOC between 30 minutes and 6 hours, an initial Glasgow Coma Scale score between 9 and 12, and PTA of less than 7 days. Of the 5 participants meeting criteria for moderate TBI, 4 had reported LOC of greater than 30 minutes and 1 reported a PTA of greater than 24 hours. No participants included in this study showed focal lesions on conventional structural magnetic resonance image.

Exclusion criteria included severe head injury (Glasgow Coma Scale score of ≤ 8); a history of other neurological disorder (eg, multiple sclerosis, tumor, seizure disorder); developmental learning disability; current (within past 30 days) substance or alcohol abuse according to *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) criteria; preinjury metabolic or other diseases known to affect central nervous system functions; or contraindication to scanning (eg, claustrophobia, shrapnel). As noted, participants with poor performance on tests of effortful engagement were excluded from analyses.

Military control group inclusion/exclusion criteria

Operation Enduring Freedom/Operation Iraqi veterans who did not meet criteria for TBI as described previously comprised the military control (MC) group. Exclusion criteria included a history of concussion or other neurological disorder; developmental learning disability; current substance or alcohol abuse according to *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) criteria; presence of a psychotic disorder or bipolar disorder as defined by *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) criteria; poor effort; or metabolic or other diseases known to affect central nervous system functions.

Measures

Neuropsychological testing was performed by trained research assistants. Administration time for the neuropsychological battery was approximately 2 hours and administration time for the mood and functional measures took approximately 15 minutes.

Neuropsychological testing

The Wide Range Achievement Test-4th Edition, Reading subtest,[43] was used as an estimate of premorbid verbal intellectual ability. The California Verbal Learning Test-II[44] was used to assess verbal memory. Variables included Trials 1–5 Total Correct, Long Delay Free Recall Total Correct, and the Recognition Discriminability Index. Visual memory was evaluated using the Rey-Osterrieth Complex Figure Test recall total score.[45] Executive functions were assessed via the total number of errors on the Wisconsin Card Sorting Test-64[46]; Delis-Kaplan Executive Function System[47] Verbal Fluency Switching total number of responses; and Delis-Kaplan Executive Function System Trail Making Test letter number switching total time.[47] The Wechsler Adult Intelligence Scale-III[48] and Wechsler Adult Intelligence Scale-IV[49] Digit Symbol subtests were used to derive a processing speed variable. Because of changes in the testing protocols, some participants received the Wechsler Adult Intelligence Scale-III version ($n = 9$) and others completed the Wechsler Adult Intelligence Scale-IV version. The basis for combining these measures lies in these 2 tests being almost identical in terms of task demands, a 0.85 Pearson correlation between versions, and no significant differences in mean age-corrected performance between the 2 measures.[49] Z scores were calculated for each domain using the grand mean and standard deviation of each test. The Test of Memory Malingering[39] and the Forced-Choice Recognition Trial of the California Verbal Learning Test-II[40] were used to assess effortful engagement in testing.

Psychological/psychosocial assessment

The PTSD Checklist–Military Version (PCL-M)[50] was used to rate the frequency and intensity of PTSD-related symptoms. Levels of depressive symptoms were assessed using the Beck Depression Inventory II.[51]

TBI interview

Each participant was asked detailed questions regarding the characteristics of his or her TBI event, including the number of TBIs he or she sustained, the number of blasts to which he or she was exposed, and whether or not he or she lost consciousness with each TBI event. Self-reported duration of LOC for any TBI event was also queried. Only 5 participants self-reported an LOC duration or PTA consistent with a moderate TBI classification, while the vast majority of TBI participants ($n = 33$) were classified as mild.

Imaging procedures

All participants underwent structural MRI and DTI on 3T General Electric magnetic resonance image scanners housed within the University of California, San Diego (UCSD) Center for Functional Magnetic Resonance Imaging on the UCSD La Jolla campus. Forty-three participants were scanned using the Excite HDx platform and, following the FMRI Center's scanner upgrade, data on 10 subjects were acquired with the scanner running the MR750 platform.

Structural scanning

A sagittally acquired high-resolution 3-dimensional T1-weighted anatomical magnetic resonance image was collected with the following parameters: field of view (FOV) 24 cm, 256 × 256 × 192 matrix, 0.94 × 0.94 × 1-mm voxels, 176 slices, repetition time (TR) = 20 ms, echo time (TE) = 4.8 ms, and flip angle of 12°. Total scan time was roughly 7 minutes.

Diffusion tensor imaging

Diffusion tensor images were collected with a dual spin echo echo planar imaging acquisition[52] with the following parameters: FOV = 240 mm, slice thickness = 3 mm, matrix size 128 × 128, in-plane resolution = 1.875 × 1.875, TR = 10900 ms, TE = 93 ms. The 10 scans from the MR750 platform used identical scanning parameters although TR was shortened to 8000 ms to reduce scan time without affecting image quality. This modification likely did not impact image signal-to-noise ratio or contrast since the TR at 8 seconds remained many times greater (>5 times) than the T1 value of the brain tissue (see Gelman et al[53]). Indeed, prior analysis of DTI signal equation modeling found that the signal to noise ratio (SNR) difference in white matter between TR 8000 ms and TR 10900 ms is only 0.007%.[54] Across scanners, 34 slices were acquired with 61 diffusion directions distributed on the surface of a sphere according to the electrostatic repulsion model[55] and a b value of 1500 s/mm^2, as well as a T2 image with no diffusion weighting ($b = 0$). Two field maps with the same spatial parameters as those of the Diffusion tensor image were collected to correct for distortions due to magnetic field inhomogeneities. Total DTI acquisition time with field mapping was roughly 12 to 16 minutes.

Image Processing

Diffusion tensor imaging data

The Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Package (FSL)[56] was used for diffusion imaging processing. The 2 field maps were used to unwarp the DTI acquisitions. In addition, a linear alignment tool to reduce the effects of gradient coil eddy currents and a 6 *df* affine motion correction for head motion were completed. Each image was visually inspected for quality and none were rejected. The FSL program *dtifit* was used on the corrected data to calculate diffusion eigenvalues and FA on a voxel-by-voxel basis. Axial diffusivity was defined as the amount of diffusion corresponding to the principal diffusion direction. Radial diffusivity was defined as the average of the 2 eigenvalues orthogonal to the principal diffusion direction. Axial diffusivity and RD are often used as proxies for estimating damage to neuronal and myelin structures, respectively.[25] Thus, increases in RD are associated with worse myelin integrity, while reductions in AD may indicate worse axonal integrity.[25] Mean diffusivity, an average of the 3 eigenvalues and an indicator of bulk diffusivity within a voxel, was not examined in this study in favor of the directional diffusivity measurements of AD and RD described previously, as these measures are more informative in terms of white matter properties that may modify measures of anisotropy.[57]

Fiber tracts were generated in TrackVis[58] following the fiber assignment by continuous tracking method.[59] To produce the fiber tracts, regions of interest (ROIs) were drawn and used as "seed points" for tractography. One rater (SFS), blind to each image's group status, drew a seed ROI (S-ROI) within each subject's color-map image for each tract. The color-map uses a color-coded scheme to display the main orientation of diffusion within each voxel. To help reduce partial voluming effects of bordering gray matter, tracking was restricted to include only those voxels with an FA value greater than .20.[60] In addition, to restrict aberrant tracking, an angle threshold of 41.4° was used.[60] This restriction limited contiguous tracking to only those voxels wherein the difference in the angle of the principal eigenvectors is less than 41.4 degrees. Fractional anisotropy, RD, and AD values from each of the tracts produced were then extracted for each subject for statistical analysis. Depictions of the tracts are shown in Figure 1.

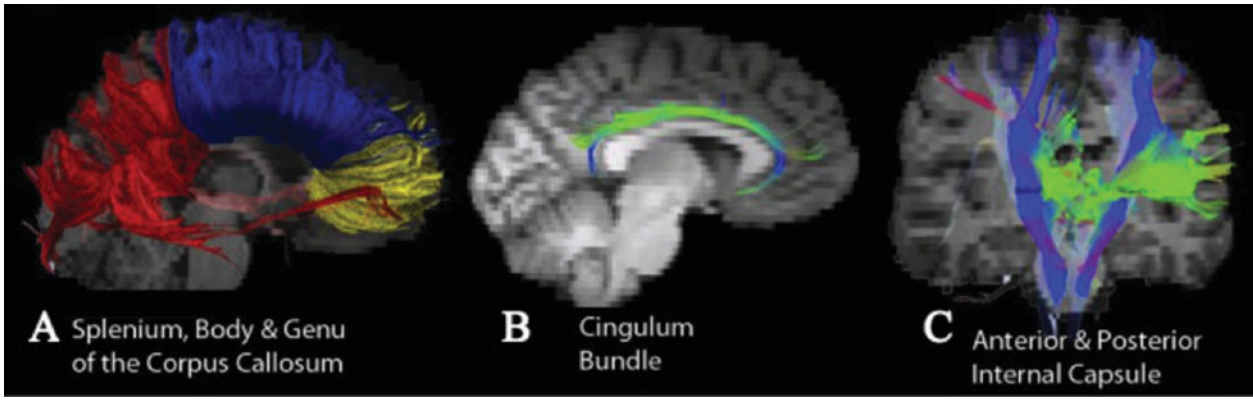

Figure 1. Diffusion tensor imaging tracts. Depiction of the white matter tracts on a representative participant with traumatic brain injury. (A) Splenium (red), body (blue), and genu (yellow); (B) cingulum bundle; and (C) anterior (green) and posterior (blue) internal capsule.

Corpus callosum

The whole of the CC was tracked by placing S-ROIs along the length of the CC, in red-colored voxels, in the midsagittal slice.[61] Corpus callosum subdivisions were identified using an adapted classification method based on cortical connectivity derived from DTI fiber tracking.[62] The posterior border of the genu was defined by a perpendicular line coursing through the anterior most point of the inner convexity. Corpus callosum voxels anterior to this line (including the rostrum and the anterior sixth of the length of the CC) represented the S-ROI for fiber tracking. The splenium was defined as the posterior fourth of the whole CC with the whole length of the CC defined as the distance from the anterior end to the posterior end. The body of the CC consisted of the middle portion bordered by the genu and the splenium as described previously.

Internal capsule

Seed ROIs were placed following published methods.[61] For the anterior internal capsule (AIC), the S-ROI was placed on the color-map image in the axial plane in green-colored voxels between the putamen and the caudate. For the posterior internal capsule, the S-ROI was placed in the axial plane in blue-colored voxels medial to the lenticular nucleus (putamen and pallidum) and lateral to the thalamus.

Cingulum

The cingulum bundle appears in the coronal plane as green voxels inferior to the cingulum gyrus and superior to the CC. To produce each cingulum tract, separate S-ROIs were placed in the anterior portion, the middle, and the posterior portion following the description of Concha et al.[63]

Intrarater reliabilities indicated strong reliability with intraclass correlation coefficients (ICC) for FA ranged from 0.70 to 0.99. Eight regions had ICCs higher than 0.85, and 7 were above 0.90. The lowest ICC value (0.70) was for the left anterior internal capsule.

Statistical analysis

Separate hierarchical regression analyses were conducted for each cognitive domain and tract to test for an effect of PTSD or TBI. Age, years of education, and BDI total score were entered in the first step, PCL-M scores were entered in the second step, and the TBI grouping variable was entered in the third step of the model. Partial correlation, χ^2 analysis, and analyses of covariance were used as indicated later. All analyses were conducted using SPSS version 22 (SPSS Inc, Chicago, Illinois).

RESULTS

Sample characteristics

As shown in Table 1, TBI and MC participants did not significantly differ with respect to most demographic characteristics except for years of education ($P = .05$). However, the groups did not differ in WRAT-4 Reading, suggesting that the difference in education was not related to differences in premorbid intellectual functioning. The TBI sample reported significantly higher levels of psychiatric distress including higher ratings on depression and PTSD symptom severity. Traumatic brain injury characteristics are also shown in Table 1. Within the TBI group, most reported experiencing more than 1 TBI event, half reported sustaining a head injury that was combat related, half reported being exposed to blast waves, and most reported LOC associated with any 1 TBI.

TABLE 1 *Sample characteristics of the military control (MC) and TBI groups*[a]

n	MC 17	TBI 38
Age (y)	33.7 (8.7)	31.2 (9.1)
WRAT-4 Reading (SS)	105.8 (9.1)	105.6 (12.2)
Years of education[b]	14.7 (2.0)	13.4 (1.4)
% Male	77	90
% White	77	55
BDI-II[c]	5.1 (8.4)	17.8 (12.5)
PCL-M[c]	22.4 (10.9)	43.0 (17.5)
Reexperiencing[c]	5.7 (2.2)	12.1 (5.6)
Avoidance/numbing[c]	9.2 (4.9)	17.3 (8.1)
Arousal[c]	7.8 (4.0)	14.4 (5.1)
Months since TBI	. . .	48.3 (31.8)
Mean number of TBIs	. . .	2.7 (2.2)
% >1 TBI	. . .	68
% Combat TBI	. . .	50
% Reporting any LOC at TBI	. . .	63
% Reporting blast-related TBI	. . .	54
No. of blasts exposed	. . .	6.9 (23.7)
No. of times dazed from blasts	. . .	2.2 (2.9)

Abbreviations: BDI-II indicates Beck Depression Inventory II; LOC, loss of consciousness; PCL-M, Posttraumatic Stress Disorder Check List-Military Version; SS, standard score; TBI, traumatic brain injury; WRAT-4, Wide Range Achievement Test, Fourth Edition.

[a]Values = mean (SD), count, or percentage (as indicated).

[b]$P < .01$.

[c]$P < .001$.

DTI tractography associations

Mean FA for each group across tracts is shown in Figure 2, and results for significant predictors of regional DTI values from the hierarchical regression analyses are shown in Table 2. After adjusting for important confounds (ie, age, education, and depression), and PCL-M score, TBI was a significant predictor of lower FA values in both the genu of the CC ($P = .03$) and in the left cingulum bundle ($P = .01$).

Mean RD for each group across tracts is shown in Figure 3. After adjusting for age, education, depression, and PCL-M score, TBI history was a significant predictor of higher RD in the left cingulum bundle ($P = .01$), right cingulum bundle ($P = .04$), and the genu ($P = .01$). PTSD Checklist–Military Version total score was not a significant predictor of DTI values in any region in models with or without the TBI grouping variable included (P values $> .23$).

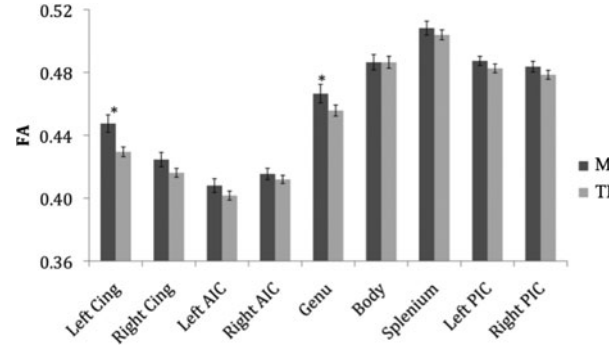

Figure 2. Regional fractional anisotropy values by group. Error bars represent standard error. [a]Groups significantly differed on hierarchical regression analysis ($P < .05$). FA indicates fractional anisotropy; MC, military control; TBI, traumatic brain injury; Cing, cingulum; AIC, anterior internal capsule; PIC, posterior internal capsule.

TABLE 2 *Regional diffusion tensor imaging indices associated with traumatic brain injury*[a]

Region	*F* (1,49)	$R^2\Delta$
Fractional anisotropy		
Genu	5.12[b]	0.09
Cingulum left	7.28[c]	0.12
Cingulum right	3.29[d]	0.06
Radial diffusivity		
Genu	7.29[c]	0.12
Cingulum left	7.73[c]	0.12
Cingulum right	4.64[b]	0.07

[a]Results of hierarchical regression predicting regional diffusion tensor imaging values (level 1: years of education, Beck Depression Inventory-II scores; level 2: Posttraumatic Stress Disorder Check-List scores; level 3: traumatic brain injury vs control).

[b]$P < .05$.

[c]$P < .01$.

[d]$P < .10$.

Associations among TBI injury characteristics and regional DTI values

Adjusting for age, education, BDI, and PCL-M scores, the number of TBIs reported was significantly negatively associated with FA in the left AIC ($\hat{\beta} = -.0027$, $t = -2.13$, $P = .04$), and right AIC ($\hat{\beta} = -.0025$, $t = -2.08$, $P = .05$). Number of blasts reported and presence of LOC were not significantly associated with regional FA, RD, or AD values (all P values $>.05$).

Correlations with PCL-M scores within the TBI group

Partial correlations, adjusting for age, demonstrated no significant correlations between FA and total PCL-M scores or PCL-M symptom subtype scores (all P values $> .05$). Contrary to expectations, RD significantly

negatively correlated with PCL-M scores in the genu ($r = -0.35$, $P = .04$). Axial diffusivity was significantly negatively correlated with PCL-M scores in the genu ($r = -0.33$, $P = .05$). Neuropsychological domain scores were not associated with PCL-M scores (all P values $>$ .05). Number of TBIs reported did not significantly correlate with PCL-M scores ($P > .86$).

Neuropsychological test performances

Z scores for the cognitive domains by group and means for individual tests by group are shown in Table 3. Traumatic brain injury history was significantly associated with poorer performances on both memory ($P = .02$) and coding ($P = .03$) measures, after adjusting for age, years of education, and BDI and PCL-M scores. In no individual models did the association between PCL-M scores and cognitive domain scores reach significance (all P values $> .05$). There were also no significant PCL-M scores by TBI interactions (all P values $>.10$) and no significant associations between number of TBIs or number of blasts with any of the neuropsychological domain scores (all P values $> .10$).

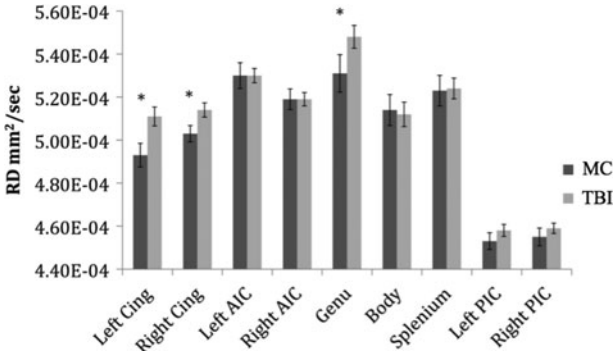

Figure 3. Regional radial diffusivity values by group. Error bars represent standard error. [a]Groups significantly differed on hierarchical regression analysis ($P < .05$). RD indicates radial diffusivity; MC, military control; TBI, traumatic brain injury; Cing, cingulum; AIC, anterior internal capsule; PIC, posterior internal capsule.

Correlations among neuropsychological domain scores and imaging variables

Significant partial correlations between neuropsychological domain scores and regional DTI variables across groups are presented in Table 4. Both processing speed and executive functions significantly correlated with FA values from multiple tracts, including those that differed between TBI and MC groups. There were no significant associations between DTI scores and the memory composite (P values $> .05$). As can be seen in Table 4, RD associations with processing speed scores were nonspecific with strong associations across 8 of the 9 tracts.

DISCUSSION

This study investigated white matter microstructure in Veterans who reported a history of mild to moderate TBI and examined whether disrupted microstructure was associated with PTSD symptom severity and cognition. Diffusion tensor imaging findings indicated that TBI history is associated with white matter damage, with disrupted microstructure in the cingulum bundles and the genu of the CC. In addition, successive mild TBIs were associated with reduced FA in bilateral anterior internal capsule regions, suggesting a dose effect of TBI. These results are consistent with the frontal susceptibility hypothesis of TBI,[16,17] and they add to the

TABLE 3 *Neuropsychological domain and individual test z scores by group*[a]

	MC	TBI	$F(1,49)$	$R^2\Delta$
Memory	0.31 (.59)	−0.11 (0.72)	5.72[b]	0.10
CVLT-II 1-5 Total	0.45 (1.03)	−0.21 (0.93)		
CVLT-II Long Delay Free Recall	0.38 (0.83)	−.17 (1.03)		
CVLT-II Recognition Discriminability Index	0.14 (1.14)	−0.06 (0.94)		
Rey-Osterrieth Delay Recall	0.09 (0.53)	−0.04 (1.16)		
Processing Speed	0.47 (0.57)	−0.24 (1.07)	5.32[b]	0.09
WAIS-IV Coding	0.54 (.53)	−0.33 (1.08)		
WAIS-III Coding	−0.53	0.07 (1.05)		
Executive functions	0.24 (0.44)	−0.13 (0.77)	1.03	0.02
WCST Total Errors	0.03 (.71)	−0.01 (1.11)		
D-KEFS Verbal Switching	0.50 (0.81)	−0.24 (1.00)		
D-KEFS Trails Switching	0.21 (.65)	−0.10 (1.12)		

Abbreviations: CVLT-II, California Verbal Learning Test, Second Edition; D-KEFS, Delis-Kaplan Executive Functioning System; MC, military control; TBI, traumatic brain injury; WAIS, Wechsler Adult Intelligence Scale.

[a]Results of hierarchical regression predicting regional DTI values (level 1: years of education, Beck Depression Inventory-II scores; level 2: PTSD Check-List scores; level 3: TBI vs Control). Values represent mean (SD)

[b]$P < .05$.

TABLE 4 *Significant partial correlations between neuropsychological domain scores and diffusion tensor imaging*[a]

	Executive functions	Processing speed
FA		
AIC right	0.27[b]	ns
Cingulum left	0.38[c]	0.38[c]
Cingulum right	0.27[b]	0.33[c]
Genu	Ns	0.44[c]
Body	0.37[c]	0.43[c]
Splenium	0.36[c]	0.31[b]
PIC left	0.51[d]	0.50[d]
PIC right	0.49[d]	0.27[b]
RD		
AIC left	ns	−0.27[b]
Cingulum left	ns	−0.40[c]
Cingulum right	ns	−0.37[c]
Genu	ns	−0.45[c]
Body	−0.30[b]	−0.48[d]
Splenium	ns	−0.36[c]
PIC left	−0.30[b]	−0.48[d]
PIC right	−0.27[b]	−0.28[b]
AD		
Body	ns	−0.29[b]
PIC right	0.32[b]	ns

Abbreviations: AD, axial diffusivity; AIC, anterior internal capsule; FA, fractional anisotropy; ns, not significant; PIC, posterior internal capsule; RD, radial diffusivity.
[a]Results of partial correlation adjusting for age.
[b]$P < .05$.
[c]$P < .01$.
[d]$P < .001$.

growing number of DTI studies linking milder grades of TBI with disrupted white matter microstructure in both civilian[27,64–66] and military samples.[35–37] Importantly, observed reductions in DTI metrics shown in the TBI group were independent of demographic differences or psychiatric symptoms, including PTSD and depression.

Although our results demonstrated that the TBI group showed far greater PTSD symptom severity than MCs, evidence in support of an association between PTSD symptom severity and disrupted white matter pathways was lacking. Current PTSD symptom ratings did not correlate with FA in any regression model, with or without inclusion of the TBI grouping variable. In addition, correlations between higher PTSD ratings and worse DTI values within the TBI group were not observed. Our results contrast with those of Bazarian and colleagues[67] and Schuff and colleagues,[15] who reported associations between PTSD and DTI values in Veterans (ie, increased diffusivity or decreased FA corresponding to increased PTSD symptoms, respectively). Differences between the DTI analytic methods of this study and those of Bazarian and colleagues[67] may, in part, account for this discrepancy. For example, Bazarian and colleagues found that the highest percentile (ie, 1st percentile) of mean diffusivity sampled across the whole of the white matter significantly correlated with PTSD severity. Such an approach may increase sensitivity to focal but spatially variable white matter variations but is limited as it does not identify where in the white matter greater diffusivity significantly corresponded with PTSD severity. The present study identified a priori identified tracts known to be affected in mTBI or with tentative links to PTSD symptoms. Schuff and colleagues[15] reported associations between the diagnosis of PTSD and FA in the anterior cingulate and white matter within the prefrontal cortex. However, their study did not stringently control for possible comorbid mTBI or blast exposure, which could also account for reduced FA in those regions, as shown in the present study. Overall, our findings align with other recent studies that have found white matter degradations associated with TBI in OEF/OIF Veterans in multiple white matter regions, including those identified in the present study (ie, the genu of the CC and cingulum white matter) but failed to find any association between regional white matter integrity and current PTSD symptoms post-TBI.[36,37]

Reductions in FA in the context of TBI are nonspecific and may be related to demyelination, axonal degeneration, or both.[68] Our findings of increased RD suggest that microstructural alterations in the TBI group are related to reductions in myelin integrity[25] and are consistent with similar reports in this regard. For example, in a sample of Veterans with blast-related mild TBI, Mac Donald and colleagues[35] found elevated RD in the cingulum bundle within 90 days of blast injury compared with controls. Study authors described a relative normalization of RD upon a follow-up scanning 6 to 12 months later, though a trend toward increased RD relative to controls persisted ($P = .07$). Our study results, however, portray a more permanent alteration in RD given our longer 4-year interval between the TBI event(s) and scanning. In another study, using macromolecular proton fraction mapping, an MRI technique sensitive to myelin, Petrie and colleagues[37] reported a diffuse pattern of abnormal myelin content associated with blast-related mild TBI. Taken together, these studies suggest dynamic changes in myelin properties following mTBI with incomplete return to baseline.

Persisting reductions in myelin integrity may explain some of the observed cognitive deficits shown in the TBI group. White matter disruption may fragment neural networks responsible for cognitive processing and, therefore, reduce functional connections among cortical and subcortical gray matter.[20] Indeed, participants with history of head trauma performed poorly on a processing speed task that requires synchronized and speeded output of many cortical and subcortical regions. The

robust correlations observed between increased RD and slower processing speed suggest that myelin compromise and concomitant slowed propagation of neuronal signaling may then contribute to reduced processing speed. However, other cognitive findings were mixed. For example, executive functions did not significantly differ between TBI and MC groups but did correlate with DTI indices across many ROIs. In addition, reduced memory performance in the TBI group compared with MCs appears to be unrelated to white matter integrity in our sample. Such findings contrast with the study by Levin and colleagues,[38] who found that worse DTI values correlated with poorer performance on a slightly more complicated word memory task than the one used in our study. It is possible that the differing task demands between the 2 measures may account for this discrepancy.

The findings of poorer processing speed and memory performances in the TBI group relative to MCs are somewhat inconsistent with the typical model of recovery following milder forms of TBI, which is characterized by a return to the normal levels within a few months postinjury,[69–72] although it has been suggested that a small percentage (10%-15%) of individuals with mTBI may experience mild but permanent cognitive deficits.[73,74] Importantly, all analyses as part of this study were conducted again, with the exclusion of the 5 participants classified as having a "moderate" TBI and the results were unchanged. Thus, any contribution of greater severity, at this level of injury, was not sufficient to account for the observed differences in cognitive functioning between MC and TBI groups in this study. Other factors, such as comorbid psychiatric distress, have been tied to complicated recovery following mTBI.[75,76] Along these lines, some studies have found that any association between mTBI and postconcussive symptom complaints and/or cognitive performance in Veteran samples is lost after accounting for psychiatric symptoms (eg, PTSD).[1,77] In the present study, the observed neuropsychological effects of TBI were independent of comorbid psychiatric distress and suggest that other factors (eg, the degree of white matter damage secondary to head injury) may be contributing to worse cognitive performance in this population.

One of the strengths of this study is that we investigated a well-characterized group of military personnel using a comprehensive cognitive battery and an imaging protocol designed to be sensitive to the effects of mTBI. In addition, we carefully excluded participants with suboptimal effort since inclusion of individuals with subthreshold scores on effort testing may exaggerate group differences on neuropsychological tests and could attenuate possible group differences on biological markers. The cognitive findings, in particular, have potential to inform clinical care as they suggest that some Veterans may indeed experience reductions in cognitive functions that persist well beyond the typical time frame associated with spontaneous recovery of about 1 year. Follow-up longitudinal studies would be necessary to determine the resiliency of these findings over time. Importantly, the findings suggest that treatment of psychiatric symptoms alone, while vital to a Veteran's health, may not be sufficient to address lingering TBI-associated cognitive reductions. Thus, additional interventions that may assist Veterans to compensate for relative reductions in cognitive abilities (eg, compensatory memory strategies)[78] may be warranted to more fully address the complex symptom profiles in this cohort of Veterans.

However, there are some limitations that warrant discussion. For example, 10 participants were scanned after the General Electric scanner upgrade; however, SNR was likely unaffected by the upgrade (as described previously), and a follow-up comparison of regional FA values between those 10 participants scanned postupgrade and 10 age-matched participants scanned preupgrade found no significant differences. This analysis did find differences in AD and RD within the genu between scanner platforms; however, the findings for this region remained after including scanner as a predictor in the regression models. In addition, the generalizability of our findings to single-event TBIs is limited as most of our participants endorsed multiple TBI events. Moreover, since our sample was on average 4 years removed from their most recent mTBI event, our finding may not extend to persons with more recent mTBI. Our assessment of PTSD symptoms also carries limitations. While the reliability of the PCL-M has been demonstrated,[79] symptom endorsement may have differed from those of a clinician-guided assessment of PTSD symptoms. Both MC and TBI groups endorsed deployments during OEF/OIF operations; however, the severity of their combat exposure was available for group comparisons. This could account for the fairly large discrepancy in the PTSD severity observed. This limitation was not thought to have greatly affected the findings of this study, and there was no correlation between PTSD symptoms and DTI values within the TBI group or when the regression analyses included both groups. Similarly, in a follow-up analysis, we found that the PTSD and depression ratings of Veterans who sustained TBIs in combat (~50% of the sample) did not significantly differ from those who reported TBIs sustained in noncombat environments (*P* values of .47-.92). Finally, the relationship between RD and myelin integrity or, membrane permeability, is indirect and susceptible to further uncertainty within highly complex white matter bundles within a voxel.[24] How white matter disruption may impact the presentation of psychiatric symptoms, including PTSD, remains an area of ongoing study, and DTI is but one of many

available measures of white matter properties. To aid in clarifying the relationship between DTI measures and white matter properties, future studies could incorporate imaging methods more directly related to myelin content.[80,81]

CONCLUSION

This study investigated whether TBI-related white matter alterations, as measured via DTI, contribute to heightened PTSD symptoms in Veterans of the recent conflicts in Iraq and Afghanistan. Our findings suggest that while TBI-related alterations of frontal white matter pathways are associated with reductions in cognitive processes (eg, processing speed), such alterations do not appear to contribute to current PTSD symptom severity. In addition, cumulative mTBIs were associated with reduced white matter integrity in bilateral anterior internal capsule regions, suggesting a dose effect of TBI. These results further support the burgeoning literature linking milder forms of head trauma to disrupted white matter microstructure. Importantly, observed reductions in DTI metrics shown in the TBI group were independent of demographic differences or psychiatric symptoms, including PTSD and depression. Taken together, these findings suggest that persisting cognitive symptoms following a history of TBI are related to white matter pathology that may be independent of comorbid psychiatric illness.

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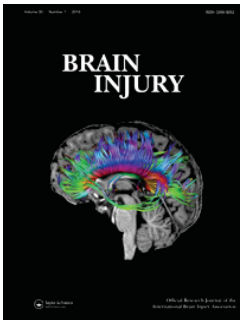

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ORIGNAL ARTICLE

Deep white matter hyperintensities affect verbal memory independent of PTSD symptoms in veterans with mild traumatic brain injury

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Abstract

Objective: Although white matter hyperintensity (WMH) pathology has been observed in the context of traumatic brain injury (TBI), the contribution of this type of macrostructural damage to cognitive and/or post-concussive symptomatology (PCS) remains unclear.
Methods: Sixty-eight Veterans (mTBI = 46, Military Controls [MCs] = 22) with and without history of mild TBI (mTBI) underwent structural MRI and comprehensive cognitive and psychiatric assessment. WMH volume was identified as deep (DWMH) or periventricular (PVWMH) on fluid-attenuated inversion recovery (FLAIR) images.
Results: Group analyses revealed that mTBI history was not associated with increased WMH pathology (p's > 0.05). However, after controlling for post-traumatic stress disorder (PTSD) and intracranial volume, DWMH was associated with reduced short-and long-delayed memory performance within the mTBI group (p's < 0.05). Additionally, after adjusting for PTSD and time since injury, regression analyses revealed that WMH was not associated with self-reported ratings of PCS (p's > 0.05) in the mTBI group.
Conclusions: The results demonstrate that, in relatively young Veterans with mTBI, DWMH differentially and negatively affects memory performance above and beyond the effects of PTSD symptoms. The findings may help to clarify prior mixed results as well as offer focused treatment implications for Veterans with history of neurotrauma and evidence of macrostructural white matter damage.

Keywords

White matter hyperintensities, white matter lesions, WMH, WML, DWMH, PVWMH, periventricular lesions, PVL, deep white matter lesions, DWML, TBI, PCS, cognition, neuropsychology, traumatic brain injury, postconcussive symptoms, head trauma

History

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Introduction

White matter hyperintensities (WMH), pathological tissue embedded within cerebral white matter, are common phenomena across the life span and, although relatively non-specific, several studies have shown that WMH are associated with both advanced age and elevated vascular risk (e.g. hypertension, smoking) [1–5]. Although little data exists in head trauma populations—particularly within military samples—recent studies of traumatic brain injury (TBI) have shown that greater WMH volume is linked to (1) worse injury severity, (2) increased cerebral atrophy and (3) decreased functional outcome on post-injury assessments of quality-of-life [6–8]. Importantly, these associations appear in both the acute (i.e. days to weeks) and chronic (i.e. months to years) phase of injury [6–8]. However, the extent to which cognition or post-concussive symptoms (PCS) are influenced by WMH in the context of TBI is not clear. Moreover, existing studies have not reported on the level of non-TBI-related WMH that may occur among individuals without TBI histories [6–9].

Although the underlying pathogenesis of WMH is not well understood [10], ageing studies have revealed dose-dependent relationships between increased WMH burden and reduced cognition [11–13]. Moreover, within the context of these studies, associations tend to differ across WMH sub-types [14–16] with *deep* white matter hyperintensities (DWMH) typically exerting more deleterious effects on neuropsychological functioning relative to *periventricular* white matter hyperintensities (PVWMH) [14,17–19]. However, whether a differential effect of WMH lesion sub-type on cognition exists has been under debate for some time (see [20]) and more research is needed to better elucidate the assocation between WMH sub-types and neuropsychological functioning. In those with history of TBI, delineation of WMH sub-types and any resultant cogntive associations may provide critical insight into cognitive deficits frequently observed in this population (e.g. memory, executive function and processing speed difficulties) [21–24]. Moreover, such explorations may increase understanding of those with history of mild TBI (mTBI) who are most likely to experience cognitive impairments that persist beyond the expected recovery window [24].

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Currently, it is unclear which lesion sub-types may play a role in the context of TBI and whether differential associations between WMH sub-type and cognitive functioning exist.

Some evidence suggests that WMH volumes may need to reach a sizeable threshold before cognitive consequences emerge [20,25–28]. However, it is not known whether this purported threshold may be reduced in the context of neurologic insults that may affect brain function, like TBI. In other words, WMH volumes may interact with history of TBI to further reduce or worsen cognitive outcome. Given their location, DWMH may be more likely than PVWMH to overlap with and impinge upon white matter tracts especially vulnerable to the shear and tensile forces that occur during TBI [29–32]. Extending this concept beyond cognition, WMH subtypes may also increase the likelihood or experience of PCS after injury [33–35]. Indeed, the presence of DWMH has frequently been linked to depression [36,37], providing some evidence that WMH pathology likely represents an important susceptibility factor for persisting negative affective, cognitive and somatic symptoms following neurotrauma. This is especially important given that a reliable biomarker of PCS has yet to be defined [33,38]. Therefore, in a well-characterized sample of Veterans with history of head trauma, this study sought to enhance understanding of WMH burden and its cognitive and behavioural associations. Specifically, it examined whether WMH pathology and its sub-types (1) differ in terms of overall severity (volume) in those with and without history of mTBI; (2) interact with history of mTBI to exert a more negative influence on cognition; and (3) are associated with PCS. Findings from this study may provide clarification about the nature of brain–behaviour relationships within the context of mild neurotrauma.

Methods

Participants

Study participants were 68 (mTBI: $n = 46$, MCs: $n = 22$) Operation Enduring Freedom, Operation Iraqi Freedom or Operation New Dawn (OEF/OIF/OND) Veterans with evidence of PVWMH and DWMH. Participants were recruited from TBI outpatient clinics at the VA San Diego Healthcare System (VASDHS) via word-of-mouth and posted recruitment fliers. All TBI participants' medical records were reviewed to confirm that they had also met criteria for mTBI during outpatient evaluations. Written and informed consent, in compliance with the institutional review boards (IRB) at the VASDHS and University of California, San Diego (UCSD) was obtained from all study participants. All participants underwent neuropsychological testing and MRI scanning at the UCSD's Keck Center for Functional MRI (CFMRI). Finally, participants completed self-report psychiatric and post-concussive symptom questionnaires.

Exclusion criteria were as follows: (1) moderate or severe TBI (i.e. loss of consciousness > 30 minutes, alteration of consciousness or post-traumatic amnesia > 24 hours or Glasgow Coma Scale > 12 [39]; (2) sub-optimal performance on tests of effort (see [40,41]); (3) prior history of neurological conditions (e.g. epilepsy, multiple sclerosis) and/or serious medical illness (e.g. myocardial infarction, stroke); (4) prior history of a learning disability; (5) current substance or alcohol abuse as determined by the *Diagnostic and Statistical Manual of Mental Disorders-IV* criteria; and (6) any contraindications that would exclude MRI.

TBI diagnostic procedure

Department of Defense (DoD) and VA TBI Task Force guidelines were utilized for diagnosis of mTBI [39,42]. These criteria are as follows: (1) presence and duration of AOC < 24 hours; (2) presence and duration of an LOC < 30 minutes; (3) presence and duration of PTA < 24 hours; and/or (4) initial Glasgow Coma Scale score (when available) of 13–15. Trained post-baccalaureate and graduate level research assistants assessed participants for any non-military (i.e. prior to or after discharge from the military) and military-related (i.e. during enlistment in the service) head injuries. Military-related injuries included the assessment of blast and blunt mechanisms of injury for each reported incident. TBI assessment was conducted via a lab-based questionnaire [43,44] modeled on the VA's semistructured clinical interview for TBI identification [45]. This interview gleans information about any falls, fights, sports-related head injuries or experiences in which the participant may have been hit or suffered a blow to the head. Critical blast-related information including the total number of blast exposures, distance, the direction from which any blast was initiated (i.e. front, back, left, right) and TBI diagnostic information (i.e. duration of LOC, AOC and PTA) were obtained via standardized prompts and open-ended questioning. Study participants were considered Military Controls (MCs) if they reported suffering no head injuries during the clinical interview, although these individuals may have been exposed to blasts.

Neuropsychological assessment

Cognitive testing included the administration of: (1) Trail Making and Verbal Fluency tests of the Delis-Kaplan Executive Function System (D-KEFS) [46]; (2) California Verbal Learning Test-2nd Edition (CVLT-II) [47], (3) Reading sub-test of the Wide Range Achievement Test-4th edition (WRAT-4) [48] and (4) the Test of Memory Malingering (TOMM) [40]. All participants completed measures of psychiatric symptomatology related to PTSD (PTSD Symptom Checklist-Military Version; PCL-M) [49] and depression (Beck-Depression Inventory-II; BDI-II) [50]. The TBI group also completed the Neurobehavioural Symptom Inventor (NSI), a self-report symptom rating scale pertaining to PCS currently being experienced [51–53]. Higher NSI scores are indicative of greater post-concussive symptoms post-injury.

Neuroimaging protocols and WMH volumetric quantification

Scans were acquired on a 3 Tesla GE Discovery MR750 whole-body scanner using an 8-channel receive-only head coil at UCSD's Center for Functional MRI (CFMRI). A sagitally acquired high-resolution 3D T1-weighted anatomical MRI was collected over ~ 8 minutes with the following

parameters: FOV = 24 cm, 256 × 256 × 192 matrix, 0.94 × 0.94 × 1.25 mm voxels, 172 slices, TR = 20 ms, TE = 3.1 ms, T1= 550, flip angle = 12°. High-resolution axially acquired T_2-weighted FLAIR images (FOV = 24.0; matrix = 352 × 244; 36 slices, flip angle = 111°, TE = 136 ms, TR = 8650 ms, T1 = 2250, 4-mm slice thickness with no inter-slice gap were also collected.

WMH volumes were quantified using previously established protocols [14,17], which were based upon previous [54] recommendations. Manual tracings were performed by one technician (NL), blind to participant characteristics and entailed volumetric tracings of roughly 17–21 axial images per subject using AFNI. Circumscribed areas of hyperintensity or areas of increased signal intensity were identified on axial slices. These measurements began on the most inferior slice in which the inferior horn of the lateral ventricle was first seen. WMH were labeled PVWMH if the largest diameter was adjacent to the ventricular lining; all other WMHs were considered to be DWMH and questionable cases involved consultation of the study neuroradiologist (MJM). WMH lesion volume was calculated by multiplying the aggregate pixel cross-sectional area in square centimetres by slick thickness in mm^3.

Statistical analyses

Given non-normal distributions of WMH in the sample (Shapiro-Wilk's test for normality: $p < 0.001$), WMH volumes underwent logarithmic transformations to improve normality. The logarithmic transformations of WMH volumes were used in all subsequent analyses. Formal group comparisons of participant characteristics and WMH volumes were conducted using analysis of variance (ANOVA) for continuous data, while all categorical data were analyses using Chi-squared analyses. Multiple hierarchical linear regressions were performed to determine whether WMH volumes were associated with differential cognitive test performance between the groups (mTBI vs MCs). Within-group analyses of PCS for the TBI group also utilized hierarchical linear regression. All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 21 (SPSS IBM, New York, NY).

Results

Participant characteristics

Participant demographics are presented in Table I. The mean education level for the mTBI group was ~ 1 year lower than that of the MCs, which was statistically significant ($p = 0.024$), although there was no difference between the groups on estimated pre-morbid intellectual functioning, as measured by the WRAT-4 Reading sub-test ($p > 0.05$). The groups also differed on sex distribution, with the MCs having a greater proportion of women than the mTBI group ($p = 0.015$). Furthermore, the mTBI group endorsed significantly greater depressive and PTSD-related symptomatology relative to the MCs (p's < 0.001). The groups did not differ on measures of vascular risk (i.e. pulse pressure), although this information was only available on a sub-set of participants (mTBI: $n = 37$, MCs: $n = 17$). Given the groups' equality on vascular measures, this was not an expected confound in WMH analyses and, therefore, not entered as a covariate in subsequent analyses.

Neurocognitive testing for the mTBI group occurred on average 57.95 months (SD = 30.72, range = 6–121 months) following the most recent mTBI. The mTBI group had on average 2.74 (SD = 1.50) mTBI events during their military careers and experienced an average of 8.10 blasts (SD = 26.32) while on deployments. The mTBI group's average total score on the NSI was 32.67 (SD = 16.86, $n = 43$), which was slightly lower than average total scores reported in similar OEF/OIF TBI samples [51].

Regional WMH pathology and associations with cognition

Non-transformed WMH volumes for each group are presented in Table I. ANCOVAs adjusting for intracranial volume (ICV)

Table I. Participant characteristics.

	TBI ($n = 46$)	MCs ($n = 22$)	F or χ^2	p
Age	30.98 (7.52)	34.05 (9.25)	2.13	0.149
Education	14.13 (1.67)	15.18 (1.92)	5.36	0.024
WRAT-4 Reading Standard Score	103.78 (12.39)	103.95 (10.39)	0.003	0.956
Gender (M:F)*	41:5	14:8	$\chi^2 = 5.89$	0.015
Ethnicity*				
Caucasian	24	15		
African American	4	1	$\chi^2 = 4.48$	0.345
Hispanic	14	3		
Asian	3	1		
Other	1	2		
BDI-II Total Score	18.07 (11.61)	3.82 (8.24)	26.63	< 0.001
PCL-M Total Score	41.35 (17.96)	20.86 (9.54)	25.10	< 0.001
Pulse Pressure (mmHg)	47.49 (9.80)	47.18 (6.62)	0.014	0.954
DWMH (mm^3)^	93.61 (254.39)	98.51 (129.04)	0.007	0.933
Median	33.46	45.02		
PVWMH (mm^3)^	255.37 (218.54)	251.72 (126.82)	0.005	0.942
Median	185.87	248.23		

* Likelihood ratio utilized; ^ non-transformed data and accompanying statistics presented; WRAT, Wide Range Achievement Test-4th Edition; BDI-II, Beck Depression Inventory-II; PCL-M, PTSD Symptom Checklist-Military Version; DWMH, deep white matter hyperintensities; PVWMH, periventricular white matter hyperintensities.

and gender revealed no significant main effects of DWMH (F (1, 64) = 0.023, p = 0.880, partial eta^2 < 0.001) or PVWMH (F(1, 64) = 0.458, p = 0.501, partial eta^2 = 0.007) volumes between the two groups. Despite group differences in psychiatric symptom severity (e.g. PTSD, depression), these variables were not included in the model given the lack of association with WMH variables (p's > 0.05) in this sample. However, sensitivity analyses revealed that the findings detailed above held when psychiatric variables were included in the model.

A series of multiple hierarchical linear regressions were performed to determine the effect of DWMH volumes on cognition for the two groups above and beyond PTSD symptoms and ICV. With respect to CVLT-II and WCST variables, accompanying norms provided demographically corrected z- and T-scores, which were entered into analyses as dependent variables. The independent variables entered into Block 1 were PCL-M total score and intracranial volume (ICV). The interaction term (i.e. Group × DWMH) was entered into Block 2. Regression analyses revealed as a significant Group × DWMH interaction for CVLT-II Short-Delay Recall (F(1, 62) = 4.191, p = 0.045, $R^2\Delta$ = 0.057, Cohen's d = 0.53) and Long-Delay Free Recall (F(1, 62) = 6.059, p = 0.017, $R^2\Delta$ = 0.082, Cohen's d = 0.54). That is, mTBI subjects with similar DWMH loads to that of the MCs performed significantly worse than MCs across both delayed memory trials (Figure 1). Furthermore, regression analyses revealed a trend towards significance for CVLT-II Trials 1–5 Total Learning T-score (F(1, 62) = 2.879, p = 0.095, $R^2\Delta$ = 0.037, Cohen's d = 0.80) such that TBI participants performed more poorly than MCs. There were no significant group interactions for WCST-64 Total Errors or Perseverative Responses (p's > 0.05). Findings did not differ across any variables when depressive symptoms were entered as an additional covariate.

With respect to D-KEFS variables, demographically-corrected scaled scores based on accompanying manual norms were again utilized as dependent variables. The independent variables entered into Block 1 were gender, education, PCL-M total score, and ICV. Again, the interaction term (i.e. Group × DWMHs) was entered into Block 2. Regression analyses revealed no significant Group × DWMH interactions for Verbal Fluency Category Switching Total or Total Time for Trails Number, Letter and Number-Letter Switching trials (p's > 0.05). Additionally, findings did not differ across any variables when depressive symptoms were entered as an additional covariate.

A series of multiple hierarchical linear regressions were performed to determine the effect of PWMH volumes on cognition for the two groups, again adjusting for PCL-M total score and ICV. Regression analyses revealed no significant Group × PVWMH interactions across any CVLT-II or WCST variables of interest (all p's > 0.05). Similarly, regression analyses for dependent D-KEFS variables in which gender, education, PCL-M total score and ICV were entered into Block 1 revealed no significant Group × PWMH for any D-KEFS variables (p's > 0.05). Moreover, findings across all cognitive variables did not differ when depressive symptoms were entered as an additional covariate.

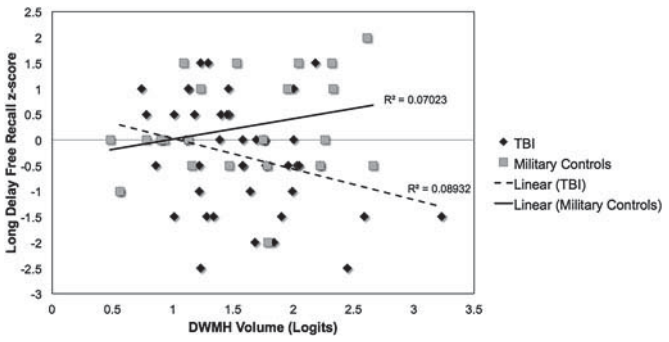

Figure 1. Group by DWMH volume scatterplot on CVLT-II long delay memory performance.

Relationship between WMH and post-concussive symptom severity

Multiple hierarchical linear regressions were performed to determine whether DWMH or PVWMH volumes predicted PCS severity within the mTBI group. The NSI total score was entered into the model as a dependent variable. Block 1 included PCL-M total score, ICV and time since most recent injury and Block 2 consisted of either DWMHs or PVWMHs volumes. Analyses revealed that neither WMH sub-type significantly predicted NSI total scores (p's > 0.05).

Discussion

To the authors' knowledge, this study represents the first to assess the contribution of regional white matter hyperintensity (WMH) burden to cognition and post-concussive symptomatology (PCS) in a cohort of relatively young military personnel with a history of mTBI. Although mTBI history itself was not associated with increased WMH pathology in this sample, DWMH volumes demonstrated a differential effect on cognition in the TBI group, even after adjustment for important covariates (e.g. post-traumatic stress symptomatology, ICV). Specifically, findings showed that greater DWMH burden was associated with worse performance on a word list-learning task in the mTBI group relative to MCs. However, contrary to expectations, WMH burden did not predict severity of PCS in this sample of Veterans with a history of mild neurotrauma.

The finding that DWMH—but not PVMH volume—was related to poorer memory performance in the mTBI group comports with several ageing studies that suggest DWMH exerts more negative effects on cognition than PVWMH [14,19,55,56]. Importantly, given their location within the deep white matter, DWMH may be associated with diminished performance on verbal memory recall due to sub-cortical disruption of vulnerable fronto-temporal white matter pathways important for memory function (e.g. uncinate fasciculus, superior longitudinal fasciculus [SLF]). Of note, the SLF is a long-coursing fibre tract that is especially vulnerable to tensile strain during mTBI [57]. While speculative, it is, therefore, possible that traumatic axonal injury (TAI)-induced abnormalities coupled with macrostructural damage to this tract may also explain the mTBI group's decreased neurocognitive test scores on delayed recall. Indeed, experimental models of TBI have demonstrated that frontal and temporal brain regions are

especially vulnerable to impact during initial insult and memory deficits have been observed across various TBI samples with frequently observed alterations in frontal and temporal white matter fibre tracts [58–60]. Importantly, observed cognitive findings in this study were independent of PTSD symptom severity, and they shed additional light on the nature of brain–behaviour relationships post-TBI. That is, in this sample of Veterans with a history of neurotrauma, white matter macrostructural damage (i.e. WMH pathology) contributes to declines in memory performance that are not better accounted for by psychiatric distress.

Interestingly, in contrast to studies conducted with ageing samples [17,19,55], DWMH pathology was related to reduced verbal memory functioning, but not slower processing speed or executive dysfunction. Recent work has suggested that there may be a certain threshold of WMH burden that predicts cognitive deficits as well as a specific phenotypic expression of impairment [25,27,61]. For example, some authors have suggested that roughly 25% of the white matter needs to be affected by WMH for dysexecutive impairment to supersede amnestic impairment [62]. It is, therefore, possible that WMH burden in this sample was not elevated enough, perhaps given the relatively young age of the sample, to negatively impact frontal-subcortical functions. Additionally, it may be that elevated WMH burden may lead to cognitive loss only when certain neural networks are disrupted and underlying pathologic processes may differ between MCI and head injured samples. Again, *where* WMHs are located—particularly in mTBI samples—may be critically important to consider [33]. Future investigations should attempt to combine multimodal imaging methods that quantify various aspect of white matter (i.e. micro- vs macrostructural) in order to more fully explore potential cognitive consequences of these types of brain changes. Additional characterization of how and to what extent WMH and its sub-types disrupt specific white matter tracts may refine and enhance one's ability to better detect brain–behaviour associations in individuals who have experienced neural insult.

Contrary to expectations, WMH volumetric differences were not found between those with and without a history of mild TBI. Interestingly, few studies examining WMH in TBI have included a control group for comparison and most existing TBI studies have not taken into account potential confounding variables such as age or cardiovascular risk factors [6–8,33,63] that are known to be related to WMH formation (see [26] for review). Additionally, in contrast to these studies, this sample consisted of a relatively homogeneous mix of injury severity, reducing potential biases of increased lesion load due to more severe injuries. Since WMH pathology is thought to reflect more severe or end-stage pathology [64], it is possible that other neurotrauma-related microstructural white matter alterations (e.g. TAI) may contribute to WMH formation with advancing age. Indeed, longtudininal studies in older adults have found that microstructural alterations contribute to greater WMH formation over time [64,65]. Additional longitudinal research is needed in order to more fully explore WMH pathology and its impact on cognitive outcomes in both TBI and non-TBI samples.

Finally, after controlling for PTSD symptoms and time since injury, there were no associations between WMH sub-types and PCS. Unfortunately, PCS are largely non-specific in nature, which greatly complicates studies of attribution. Within Veteran samples, the presence and severity of PCS has been repeatedly linked to psychiatric distress and Veterans with co-morbid PTSD and mTBI diagnosis are more likely to report increased rates of PCS than either condition alone [66–69]. As such, PCS may represent an unreliable estimate of neurological functioning within the context of co-morbid psychiatric distress—especially when the head injury event is remote [70]—and may lead to misattribution of these relatively non-specific symptoms to TBI [71]. However, the association is still unclear, as significant PCS and white matter microstructural abnormalities gleaned using diffusion tensor imaging (DTI) have been observed in other Veteran samples with comorbid PTSD -and/or depression [72]. Given the considerable overlap between PTSD and PCS complaints, potential associations between WMH subtypes and PCS should be explored in samples without significant psychiatric symptoms. Moreover, as previously noted, depending on the overal burden and anatomical location of WMH pathology within specific functional tracts, the perceived severity of neuropsychiatric and cognitive sequealae likely varies from indiviual to individual.

This study affirms that white matter macrostructural alterations (i.e. WMH) should be considered clinically in the context of neurotrauma and additional studies in this area are greatly needed. However, there are some weaknesses of this study that should be noted. First, the MCs group was smaller than the TBI group, which may have attenuated any potential associations between WMH sub-types and cognition in the group analyses, although the moderate effect sizes lessen this concern. The MCs group also suffered from relatively minimal psychiatric symptoms and may not be entirely representative of the Veteran population. As such, sampling bias must be considered, as this was largely a sample of convenience. Finally, despite no differences in blood pressure measures, use of more sophisticated physiological measurements may have yielded different results, since WMH have been closely associated to vascular risk factors [54,73–75].

Conclusion

To the authors' knowledge, this is the first study to examine WMH sub-types and their effects on cognition and PCS in well-characterized samples of Veterans with and without a history of mTBI. Results showed an interaction such that DWMH pathology had a more negative impact on memory performance in those with mTBI relative to Veterans with no history of neurotrauma. However, contrary to expectations, WMH burden was not related to PCS severity in this sample. Additional multimodal, multidisciplinary research is needed in order to clarify the long-term effects of DWMH pathology in those with a history of neurotrauma, especially in the context of advancing age. Collectively, the results suggest that WMH pathology, particularly when occurring within the deep white matter, should be considered within the context of TBI and findings suggest that, even in relatively young adults, DWMH burden contributes to reductions in memory performance independent of PTSD symptoms within mTBI.

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Problem alcohol use in veterans with mild traumatic brain injury: Associations with cognitive performance and psychiatric symptoms

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ABSTRACT

Introduction: Given that little is known about the associations between alcohol use, cognition, and psychiatric symptoms among veterans with a history of mild traumatic brain injury (mTBI), we aimed to (a) characterize how they differ from veteran controls on a measure of problem drinking; (b) investigate whether problem drinking is associated with demographic or mTBI characteristics; and (c) examine the associations between alcohol use, mTBI history, psychiatric functioning, and cognition. *Method*: We assessed 59 veterans (n = 32 with mTBI history; n = 27 military controls) for problem alcohol use (Alcohol Use Disorders Identification Test: AUDIT), psychiatric symptoms, and neuropsychological functioning. *Results*: Compared to controls, veterans with mTBI history were more likely to score above the AUDIT cutoff score of 8 (p = .016), suggesting a higher rate of problem drinking. Participants with mTBI history also showed elevated psychiatric symptoms (ps < .001) and lower cognitive scores (ps < .05 to < .001). Veterans with higher AUDIT scores were younger (p = .05) and had less education (p < .01) and more psychiatric symptoms (ps < .01), but mTBI characteristics did not differ. After controlling for combat and mTBI history (R^2 = .04, *ns*) and posttraumatic stress disorder (PTSD) symptoms (ΔR^2 = .08, p = .05), we found that higher AUDIT scores were associated with poorer attention/processing speed, $F(9, 37) = 2.55$, p = .022; ΔR^2 = .26, p = .03. *Conclusions*: This preliminary study suggested that veterans with mTBI history may be at increased risk for problem drinking. Problem alcohol use was primarily associated with more severe PTSD symptoms and poorer attention/processing speed, though not with combat or mTBI characteristics per se. Importantly, findings emphasize the importance of assessing for and treating problematic alcohol use and comorbid psychiatric symptoms among veterans, including those with a history of neurotrauma.

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Among veterans who served in the Iraq and Afghanistan wars [Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF), and Operation New Dawn (OND)], mild traumatic brain injury (mTBI) is considered the "signature injury" of those conflicts. Estimates of the prevalence of TBI vary between samples. For example, in 2009 approximately 7% of OEF/OIF veterans using Veterans Health Administration services had a TBI diagnosis (Taylor et al., 2012). Other estimates of TBI among U.S. Army soldiers returning from deployment in Iraq range from 15% (Hoge et al., 2008) to about 23% within a combat unit (Terrio et al., 2009), and the majority of TBIs were of mild severity. The prevalence of TBI during the Persian Gulf War is less well known, but one study of Gulf War veterans found that 12% endorsed a history of TBI (Yee et al., 2015). Additionally, of those with neurotrauma, many often have a comorbid psychiatric diagnosis (primarily posttraumatic stress disorder, PTSD) and co-occurring pain.

Meta-analytic studies suggest that, on average, most people recover from the acute cognitive effects of mTBI within a few days to 3 months after head

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injury (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005; Frencham, Fox, & Mayberry, 2005), except in clinical samples or with those involved in litigation where the effects were stable or worsened (Belanger et al., 2005). A subset of individuals with mTBI continue to have complaints of cognitive, somatic, and emotional symptoms for months or years post head injury (known as "post-concussive syndrome"), such as veterans who have a history of PTSD (Vanderploeg, Belanger, & Curtiss, 2009). Karr, Areshenkoff, Duggan, and Garcia-Barrera (2014) also found subtle long-term negative effects of blast-related military mTBI on cognition, particularly for executive functioning (set-shifting), with an average of 3.79 years since head injury. Studies of various populations suggest that the cognitive sequelae following mTBI may include deficits across several domains, such as processing speed (Frencham et al., 2005; Levin et al., 2013), attention, language, learning and memory (Belanger et al., 2005; Mathias, Beall, & Bigler, 2004; Sozda, Muir, Springer, Partovi, & Cole, 2014), and executive functioning (Sorg et al., 2014; for review, see Dolan et al., 2012; for a meta-analysis, see Karr et al., 2014).

Indeed, assessment of the consequences of mTBI is complicated by several factors, including range in severity of injury, duration of cognitive symptoms, length of time between the injury and neuropsychological testing (if evaluated medically at all), the co-occurrence and overlap in symptoms of mTBI and PTSD (particularly in military populations), and issues of effort and the possibility of secondary gain (see Armistead-Jehle, 2010; Dolan et al., 2012). With regard to comorbid psychiatric concerns, Vasterling et al. (2012) reported that PTSD and depression were related to reduced cognitive performance and poorer somatic and cognitive health outcomes, and others reported that PTSD or depressive symptoms were more strongly related to cognitive performance than mTBI history (Neipert et al., 2014; Nelson et al., 2012; Sozda et al., 2014). Collectively, these study findings emphasize the importance of examining the associations of mTBI and head injury characteristics with PTSD, depression, and effort during neuropsychological testing.

An additional variable to consider within the military population is the high prevalence of heavy/binge alcohol use and alcohol-related problems. Analysis of the 2005 Department of Defense Survey of Health Related Behaviors Among Military Personnel showed that 43% of active duty military personnel reported binge drinking within the past month (Stahre, Brewer, Fonseca, & Naimi, 2009). Findings were especially robust for personnel who were younger (17–25 years old), male, White or Hispanic, who were in the Marines or Army, and who had a high school education or less (e.g., Jacobson et al., 2008; Stahre et al., 2009). Although men are at higher risk for binge drinking (i.e., 5+ drinks/occasion for men; 4+ drinks for women) and alcohol-related problems (e.g., drinking despite being asked to cut down; drinking, being high, or hungover from alcohol at work; being late or missing activities due to drinking; or driving while intoxicated), Jacobson and colleagues (2008) showed that military women also reported heavy drinking (7+ drinks/week for women, 12+ drinks/week for men). Additionally, the findings of Jacobson et al. (2008) demonstrated that exposure to combat during deployment increased risk for heavy drinking, and that new-onset problem drinking was associated with a high comorbidity with depression and PTSD (related to combat-exposure or military sexual trauma), other mental health issues, and/or psychiatric medication use (Jacobson et al., 2008; see Schumm & Chard, 2012, for review). Of great concern is that binge drinkers tend to report more adverse consequences, such as problems at work (e.g., not getting promoted, working below normal level), driving while intoxicated, getting into fights, risk-behaviors, injuries, and legal problems (Stahre et al., 2009), which may have long-term consequences. Further, alcohol misuse can interfere with recovery from posttraumatic stress (see Schumm & Chard, 2012, for review).

Alcohol misuse may be especially problematic in military personnel who have experienced neurotrauma. According to Miller et al. (2013), active duty airmen who sustained an mTBI showed an increased risk of alcohol dependence compared to airmen with other types of physical injury. The risk for alcohol dependence remained over the subsequent year following TBI, suggesting that it is a significant health problem for vulnerable military personnel with head trauma. Adams, Larson, Corrigan, Horgan, and Williams (2012) also found an increased risk of frequent binge drinking among active duty military personnel with a recent TBI history, compared to those without injury or TBI. Similarly, Heltemes, Dougherty, MacGregor, and Galarneau (2011) compared blast-injured combat service members with versus without mTBI. mTBI participants were slightly more likely to have a diagnosis of alcohol-use disorder, although this did not reach statistical significance. As with previous research, younger service members demonstrated

higher rates of alcohol-related diagnosis than their slightly older cohorts. Importantly, continued or increased alcohol misuse following a TBI may impede recovery and place service members at higher risk for possible longer term negative outcomes from heavy drinking (see review by Adams, Corrigan, & Larson, 2012).

Despite the prevalence of mTBI, PTSD, and alcohol misuse in the military, the associations between problematic alcohol use, psychiatric symptoms, and cognition have not been explored in the veteran mTBI population. In a nonmilitary civilian sample, Lange, Iverson, and Franzen (2007) found that preinjury alcohol abuse had a mild effect on postinjury short-term (within 7 days) neuropsychological performance in uncomplicated mTBI, especially for those who were intoxicated at the time of injury (cf., Lange et al., 2014). In a civilian moderate to severe TBI population, preinjury harmful or hazardous alcohol use was associated with poorer memory and processing speed, while heavier past month alcohol use was associated with poorer executive functioning (Ponsford, Tweedly, & Taffe, 2013). Earlier studies in civilian populations have also reported poorer neuropsychological performance, at least in the short term, for individuals intoxicated at the time of injury (for a review, see Parry-Jones, Vaughan, & Cox, 2006). Further, the cognitive profiles of mTBI patients can be difficult to distinguish from those of patients with substance use disorders. For example, heavy, chronic alcohol use is associated with decrements in executive functioning, memory, processing speed, and visuospatial skills, mirroring studies of cognition in TBI (Bates, Voelbel, & Buckman, 2005; Fein, Bachman, Fisher, & Davenport, 1990; Fein, Torres, Price, & Di Sclafani, 2006; Hanson, Medina, Padula, Tapert, & Brown, 2011). When individuals with mTBI were compared to non-TBI patients receiving treatment for substance use disorders, no reliable differences could be detected between these two groups (Iverson, Lange, & Franzen, 2005; Lange, Iverson, & Franzen, 2008). Likewise, TBI patients with and without a history of alcoholism both performed worse than a patient comparison group but did not differ from each other (Allen, Goldstein, Caponigro, & Donohue, 2009).

To our knowledge, this preliminary study represents the first to examine the associations between alcohol use, psychiatric functioning, and cognition in a military/veteran mTBI population. Specifically, we aimed to (a) characterize how a sample of veterans with a history of mTBI differed from military veteran controls on a commonly used clinical screening measure of problem drinking (*Alcohol Use Disorders Identification Test*, or *AUDIT*; Saunders, Aasland, Babor, de la Fuente, & Grant, 1993); (b) investigate whether problem drinking is associated with specific demographic or mTBI characteristics; and (c) examine how combat history, mTBI history, psychiatric functioning, and cognitive performance are associated with AUDIT scores.

Method

Participants

Fifty-nine participants were included in the current study (mTBI: n = 32; military controls, MCs, with no history of TBI: n = 27; see Table 1 for key demographic information), which stemmed from a larger, ongoing longitudinal study on traumatic brain injury. All but two participants were veterans (1 mTBI and 1 MC were active duty). However, the terms "military" and "veteran" are used somewhat interchangeably throughout the manuscript. All participants completed a written informed consent process, and all study procedures complied with the local University and Veterans Affairs institutional review boards.

Veterans were recruited through (a) fliers or brochures distributed in clinics or within the general hospital areas at the Veterans Affairs San Diego Healthcare System (VASDHS) or at veteran organizations throughout San Diego, such as at community colleges, (b) referrals following formal clinical neuropsychological assessment at the VASDHS, or (c) referrals from other research studies at VASDHS or the San Diego Veterans Medical Research Foundation (e.g., PTSD research, women veterans study, other TBI studies). Study fliers advertised a "Concussion & Brain Imaging Research Study" or a "Brain Imaging, Cognition, & Fatigue Study" that included questionnaires, brain imaging, and cognitive testing. For individuals who completed neuropsychological testing at the VASDHS in the previous 6 months, testing was not repeated but was supplemented with additional study measures not already administered in order to avoid practice effects. Although this approach may have added some variability to the clinical and neuropsychological associations because of the disparate data collection sessions, our goal was to maximize use of the available clinical data while minimizing data collection redundancies and practice effects. Inclusion criteria were essentially the same as those in the larger longitudinal study; specifically, veterans between the

Table 1. Demographic characteristics and psychiatric symptoms among veterans with a history of mTBI versus military veteran controls.

Demographics and psychiatric symptoms	MC (n = 27)	mTBI (n = 32)	F, or Fisher's exact
Age (years)	33.70 (8.15)	29.81 (7.63)	3.58
Education (years)	14.89 (1.91)	13.91 (1.82)	4.08*
Gender (no. female: no. male)	8F:19M	2F:30M	*
Race (% Caucasian)	70	44	13.21**
% Married/cohabitating	48	42	*ns*
Branch of service (%)			8.87*
Navy	38	16	
Army	15	28	
Marines	35	53	
Air Force	12	0	
National Guard	0	3	
% OEF/OIF/OND veterans[a]	74	94	*ns*
% Deployed[b]	92	97	*ns*
% Saw combat	56	84	*
Mood/behavior total scores			
BDI	4.85 (8.21)	18.28 (11.17)	27.79***
BAI	2.59 (3.48)	13.29 (10.52)	25.43***
PCL–M	21.52 (8.95)	44.63 (18.48)	35.16***

Note. Values are means (and standard deviations) unless otherwise noted. MC = military controls; mTBI = mild traumatic brain injury; OEF/OIF/OND = Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn; BDI = Beck Depression Inventory; BAI = Beck Anxiety Inventory; PCL–M = Posttraumatic Stress Disorder Checklist–Military Version.
[a]The remaining veterans were from the Persian Gulf War era. [b]All but 1 mTBI and 2 MC participants were deployed during their active military service. Results were comparable when the 3 nondeployed participants were excluded.
*p < .05. **p < .01. ***p < .001. *ns* = not statistically significant.

ages of 18 and 53 years with a history of mTBI within the past 8 years were included in the head injury group. We included TBI participants who reported that their most significant TBI occurred at age 18 or older and was of mild severity.

With the use of a structured clinical interview administered by trained research assistants, participants were interviewed in detail about any history of falls, fights, sports-related head injuries, and any other situation(s) in which they experienced a TBI event. Endorsement of any of these experiences led to additional questioning regarding TBI symptoms. Veterans reporting no history of TBI were eligible for the military control group. All mTBI participants were diagnosed with a mild closed head injury using criteria delineated by the Department of Defense (DoD) and Department of Veterans Affairs Traumatic Brain Injury Task Force (Traumatic Brain Injury Task Force, 2008) for mTBI. Briefly, the criteria for mTBI include at least one of the following: (a) loss of consciousness (LOC) lasting ≤30 min; (b) alteration of consciousness (AOC) or posttraumatic amnesia (PTA) of ≤24 hours; (c) an initial Glasgow Coma Scale (GCS score) between 13 and 15; and/or (d) neurological deficits that may or may not be transient (e.g., weakness, balance disturbance, sensory alterations). A TBI diagnosis did not require LOC, as an AOC of less than 24 hours subsequent to a head injury fulfilled the DoD diagnostic criteria (Casscells, 2007). Because medical records pertaining to mTBI events are usually not available, particularly in combat settings, we gathered LOC, AOC, and PTA information through self-report. GCS scores were typically not available. In addition to PTA, AOC, LOC, and conditions of the injury (e.g., source, timing, and environment of injury), participants provided information on their "worst" or "most significant" head injury, as determined by their self-reported durations of LOC and PTA. We also recorded the total number of TBI events, the number of blast events reported (with or without injury), and the number of blunt force mTBI events that occurred during deployment.

Because this study was conducted as part of a larger study that was not specifically designed to examine the effects of problem substance use and to reduce the possible effects of very heavy substance use on outcome measures (e.g., chronic alcohol dependence; heavy marijuana, stimulant, or depressant use), we screened out individuals meeting *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., *DSM–IV*; American Psychiatric Association, 2000) criteria for current (within 30 days) alcohol or other substance abuse, or lifetime history of substance dependence. Further, we excluded individuals with a history of

heavy illicit drug use (e.g., cocaine, methamphetamine, heroin, ecstasy) and with use of marijuana or other drugs within the past four weeks.

Additional exclusion criteria for all mTBI and MC participants included (a) a positive toxicology screen on the testing day from a 14-drug panel; (b) moderate to severe TBI (LOC >30 minutes, PTA or AOC >24 hours, GCS score ≤12); (c) a lifetime history of other neurological condition (e.g., multiple sclerosis, seizure disorder); (d) preinjury metabolic or other diseases that may affect cognition (e.g., diabetes); (e) for women, current or possible pregnancy (exclusion due to brain imaging conducted as part of the study protocol; data not included here); (e) involvement in current or pending litigation; (f) a developmental learning disability; and (g) current or previous history of bipolar disorder, schizophrenia, or other psychotic disorders, active psychotic symptoms, or suicidal ideation. We did not exclude individuals with history of depression, anxiety, or PTSD unless study participation was otherwise contraindicated, as these conditions frequently occur among veterans with TBI. Similarly, we also did not exclude participants undergoing psychotherapy or taking psychotropic medications for these conditions. In particular, some participants were prescribed antidepressants (10 mTBI, 3 MCs; including selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, norepinephrine reuptake inhibitors, or tricyclic antidepressants), anxiolytics (5 mTBI, 1 MC; benzodiazepines, buspirone, propranolol), and sleep aids (5 mTBI, 2 MCs; zolpidem, trazodone, temazepam). Five participants with mTBI and 1 MC were prescribed pain medications (baclofen, vicodin, tramadol, gabapentin). Finally, 1 mTBI participant was prescribed nicotine replacement therapy, and 3 MCs were prescribed psychostimulants (Adderall, Ritalin). The groups did not significantly differ in their medication use (Fisher's exact test, $ps > .05$). Finally, we excluded individuals who scored below cutoff scores on neuropsychological effort testing, as described below.

The resulting sample of participants with mTBI were tested an average of about 4 years following their most significant TBI event (mean = 51.10 months; *SD* = 24.96 months; range = 8–93 months). All participants were less than 8 years from the date of their most significant mTBI event. Mild TBI participants had a mean of 2.44 reported mTBI events (*SD* = 1.46, mode = 2, range = 1–8). With regard to mechanism of the most significant mTBI, 21.9% were blast-related, 56.3% were from blunt force, and 15.6% were characterized as a blast-related injury with a secondary/tertiary blunt force. Veterans with mTBI reported a mean of 7.80 blast events (with or without injury; mode = 0–1) and, on average, <1 blunt event that occurred during deployment (mode = 0). Further, 69% reported having sustained an mTBI during combat, but just 50% reported that their most significant mTBI occurred during combat. Approximately 65.6% reported an LOC (mean for most severe mTBI LOC = 6.62 min., *SD* = 9.61), while 34.4% reported experiencing an AOC (mean for most severe mTBI AOC = 1.26 min., *SD* = 1.38), and 34.4% reported PTA (mean for most severe mTBI PTA = 1.64 min., *SD* = 3.93).

Alcohol use screen

To assess for alcohol-related problems, we utilized the Alcohol Use Disorders Identification Test (AUDIT), which is a brief screening instrument in wide use in both clinical and research settings (Saunders et al., 1993). This 10-item questionnaire assesses for amount and frequency of alcohol use and alcohol-related problems in the past year, including being unable to stop drinking, drinking in the morning after a night of heavy drinking, failure of obligations due to alcohol use, guilt or remorse about alcohol use, being unable to remember events that occurred while intoxicated (blackouts), injury relating to alcohol use, and other people expressing concern regarding alcohol use. Each item is rated 0–4 (higher score = more problematic use), and items are summed for the total score. We used a recommended cutoff score of 8 to identify veterans with problematic alcohol use (Conigrave, Hall, & Saunders, 1995; Conigrave, Saunders, & Reznik, 1995). Using this cutoff score, the sensitivity for detecting harmful or hazardous alcohol use has been reported as 92%, with a specificity of 94%, and it correctly identified 99% of individuals with alcohol use disorder in an external reference group (Saunders et al., 1993). For the current sample, 9/32 mTBI participants were classified as having AUDIT scores above the cutoff, compared to 1/27 MCs.

Neuropsychological assessment

Trained neuropsychometrists completed a 240-min standardized neuropsychological (NP) battery individually with each participant. Tests included Trail Making and Verbal Fluency subtests from the Delis–Kaplan Executive Functioning System (D-KEFS;

Delis, Kaplan, & Kramer, 2001); Logical Memory and Visual Reproduction subtests from the Wechsler Memory Scale–Third or Fourth Editions (WMS–III and WMS–IV; Wechsler, 1997b; Wechsler, 2009); California Verbal Learning Test–Second Edition (CVLT–II; Delis, Kramer, Kaplan, & Ober, 2000); Block Design subtest from the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) or Wechsler Adult Intelligence Scale–Third Edition (WAIS–III; Wechsler, 1997a); Digit Span and Symbol Search subtests from the WAIS–III or Wechsler Adult Intelligence Scale–Fourth Edition (WAIS–IV; Wechsler, 2008); WAIS–IV Digit Symbol Coding subtest; and the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983) and Grooved Pegboard test (Lafayette Instrument, 1989) from the Expanded Halstead–Reitan Neuropsychological Battery (HRNB). We used the Reading subtest from the Wide Range Achievement Test–3 or Wide Range Achievement Test–4 (WRAT–3 and WRAT–4; Wilkinson, 1993; Wilkinson & Robertson, 2006) as a measure of premorbid intellectual functioning.

Raw scores were not available for all participants or were not equivalent given the different versions of some tests administered during the course of this study (e.g., WAIS–III or WAIS–IV). Therefore, demographically adjusted *t*-scores and scaled scores were used for all analyses, with the exception of WAIS–III/WAIS–IV Digit Span, which was separated into "Digits Forward" and "Digits Backward" to measure auditory attention and verbal working memory, respectively. Because demographically corrected normative scores were not available individually for Digits Forward and Digits Backward (only for Digit Span Total Score), we calculated age-corrected standardized residual scores for these two measures. No differences in performance were found between the various test versions (e.g., WAIS–III versus WAIS–IV).

Neuropsychological data reduction

With the goal of reducing the number of comparisons and possible Type I error, we combined subtests to create average scores within each domain. As with previous publications (e.g., Hanson & Luciana, 2010; Hanson et al., 2011), we used a hybrid method that considered established cognitive domains (Lezak, Howieson, Bigler, & Tranel, 2012) and reliability analyses (Delis, Jacobson, Bondi, Hamilton, & Salmon, 2003). This approach avoids some of the limitations associated with shared variance techniques, such as correlations or factor analysis, in creating composite scores (Delis et al., 2003). We then confirmed the internal consistency reliability of each of the composites via Cronbach's α coefficients (Cronbach, 1951).

First, we created standardized scores (*z*-scores) for each subtest, with higher standard scores representing better performance. Next, we grouped the subtests to form distinct cognitive domains (Lezak et al., 2012) and calculated the mean of the combined standard scores within each domain. We then computed standardized Cronbach's α coefficients to measure the internal consistency reliability of the tests that made up each composite score. For composite scores that yielded Cronbach's α coefficients below .60, we added or removed tests until we achieved "good" reliability (i.e., α = .7 to .9). In two cases, the neuropsychological measure was best represented by standing alone (i.e., Boston Naming Test *t*-score and WASI/WASI–II Block Design *t*-score). Using this method, we derived six summary scores representing performance in each cognitive domain. Cronbach's α for each composite score ranged from .73 to .82:

(1) Executive functioning (α = .73).
   a. D-KEFS Verbal Fluency: Letter Fluency, Category Fluency, and Category Fluency Switching subtests age-corrected scaled scores.
   b. D-KEFS Trail Making Number–Letter Switching subtest age-corrected scaled score.
   c. WAIS–III/WAIS–IV Digit Span backward score (age-corrected standardized residual score).
(2) Learning and memory (α = .77).
   a. WMS–III/WMS–IV Logical Memory: Immediate and Delayed Recall age-corrected scaled scores.
   b. WMS–III/WMS–IV Visual Reproduction: Immediate and Delayed Recall age-corrected scaled scores.
   c. CVLT–II: Trials 1–5 total score (*t*-score) and Long Delay Free Recall *z* score.
(3) Attention and processing speed (α = .82).

a. WAIS–III/WAIS–IV Digit Span forward score (age-corrected standardized residual score).
b. WAIS–III/WAIS–IV Symbol Search and Digit Symbol Coding age-corrected scaled scores.
c. D-KEFS Trail Making Test: Visual Scanning, Number Sequencing, Letter Sequencing, and Motor Speed subtests age-corrected scaled scores.

(4) Visuospatial construction: WASI/WASI–II Block Design *t*-score.
(5) Language: Boston Naming Test *t*-score. and
(6) Manual motor dexterity (α = .79): Grooved Pegboard test average of dominant and nondominant hand *t*-scores.

Symptom validity test measures

We used the Test of Memory Malingering (TOMM; Tombaugh, 1996) and the Forced-Choice Recognition Trial of the California Verbal Learning Test–II (Delis et al., 2000) to assess effort on cognitive testing. Cutoff scores were based on recommendations from Tombaugh (1996) and Moore and Donders (2004), respectively. Individuals performing below cutoffs on either cognitive symptom validity test were excluded from this study (n = 12 participants); mTBI participants were more likely to be excluded for this reason than controls (n = 11 mTBI and 1 control; Fisher's Exact, p = .02).

Mood/behavioral symptom self-report inventories

The Posttraumatic Stress Disorder Checklist–Military Version (PCL–M; Weathers, Litz, Herman, Huska, & Keane, 1993) was used to measure symptoms of PTSD. We administered the Beck Depression Inventory–II (BDI–II; Beck, Steer, & Brown, 1996) to assess current (past two weeks) level of depressive symptoms, and we used the Beck Anxiety Inventory (BAI; Beck & Steer, 1990) to measure levels of anxiety.

Statistical analyses

First, we used the nonparametric Mann–Whitney procedure to detect group differences on the AUDIT total score and to examine any differences in responding on the 10 individual items of the AUDIT. We used Fisher's exact test to compare groups on the likelihood of scoring above or below the AUDIT cutoff score of 8. Further, we employed analysis of variance (ANOVA) and Fisher's exact tests to compare high AUDIT scorers (at or above cutoff of 8) to low AUDIT scorers (7 or less) on demographics, psychiatric functioning, deployment and combat history, and mTBI characteristics. Next, the six cognitive domain z scores were compared between groups using ANOVA to illustrate overall performance prior to examining associations with other variables. We also conducted a follow-up analysis using PCL–M score as a covariate to examine the role of PTSD symptoms in cognitive test performance. The PCL–M was chosen as the psychiatric covariate because of the prevalence of PTSD in veterans with mTBI (e.g., Vanderploeg et al., 2009), because the current sample showed the largest group difference on this psychiatric measure, and to avoid symptom overlap with other psychiatric measures. We opted not to control for age and education in NP data analyses given our use of demographically corrected NP scores and comparable levels of premorbid intellectual functioning. We then used a four-step hierarchical multiple regression to examine associations of combat and mTBI history, PTSD symptoms, and cognitive performance with AUDIT scores (log transformed to meet the requirements for parametric analysis), entering combat history (Block 1; 0 = no, 1 = yes), mTBI history (Block 2; 0 = no mTBI history, 1 = history of at least one mTBI), PCL–M score (Block 3), and the six cognitive domain z scores (Block 4). Finally, we conducted Pearson correlations to further examine the relationships between the variables included in the regression analysis. Interpretations of statistical significance were made if $p < .05$, although some trends are also described ($p < .10$). We conducted all analyses using the Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL, USA), Version 23.0 for Windows.

Results

Group differences on self-reported problem alcohol use

Veterans with mTBI history scored higher on the AUDIT total score than MCs (Mann–Whitney U = 301.0, p = .044); likewise, veterans with mTBI were more likely to score above the cutoff score of 8 on the AUDIT (Table 2; Fisher's Exact test, p = .016). Upon examination of individual items on the AUDIT, veterans with mTBI history scored higher on Item 8

Table 2. Scores on the Alcohol Use Disorders Identification Test for veterans with mTBI history compared to MCs with no TBI history.

Group	AUDIT score Mean (*SD*)	Below AUDIT cutoff %	Above AUDIT cutoff %
mTBI	5.50 (6.03)*	72	28*
MCs	2.41 (2.52)	96	4

Note. AUDIT = Alcohol Use Disorders Identification Test; MCs = military controls; mTBI = mild traumatic brain injury. Veterans with mTBI history are more likely to score above cutoff score of 8 on the Alcohol Use Disorders Identification Test compared to MCs with no TBI history.*
*$p < .05$.

(Mann–Whitney $U = 312.5$, $p = .012$; i.e., "How often in the last year have you been unable to remember what happened the night before because of drinking?") and Item 10 (Mann–Whitney $U = 351.0$, $p = .019$; i.e., "Has a friend, relative, or doctor or other health worker ever been concerned about your drinking or suggested you cut down?").

Demographic and mTBI characteristics among high AUDIT scorers

While recognizing that alcohol behaviors are often continuous, ranging from no problems to severe problems, we examined the AUDIT cutoff scores to provide practitioners with useful heuristics when working with similar populations. Collapsed across the entire sample, we found that veterans who scored above (high AUDIT; $n = 10$) versus below (low AUDIT; $n = 49$) the AUDIT cutoff score were about 5 years younger [high AUDIT: $M = 27.10$ years, $SD = 4.38$; low AUDIT: $M = 32.51$ years, $SD = 8.34$; $F(1, 57) = 3.95$, $p = .05$], had an average of 2 fewer years of education [high AUDIT: $M = 12.80$ years, $SD = 1.03$; low AUDIT: $M = 14.67$ years, $SD = 1.90$; $F(1, 57) = 9.11$, $p = .004$], and had higher self-reported symptoms of PTSD [PCL–M; high AUDIT: $M = 48.90$ (clinical range), $SD = 14.81$; low AUDIT: $M = 31.02$ (nonclinical range), $SD = 18.18$; $F(1, 57) = 8.48$, $p = .005$], depression [BDI; high AUDIT: $M = 22.60$ (moderate range), $SD = 12.14$; low AUDIT: $M = 10.00$ (nonclinical range), $SD = 10.82$; $F(1, 57) = 10.83$, $p = .002$], and anxiety [BAI; high AUDIT: $M = 17.50$ (moderate range), $SD = 9.74$; low AUDIT: $M = 6.40$ (nonclinical range), $SD = 8.52$; $F(1, 57) = 13.39$, $p = .001$]; they did not differ on other demographic variables. Among veterans with mTBI histories, those who scored above versus below the AUDIT cutoff did not differ on specific mTBI characteristics (i.e., total number of mTBI events reported; time since most significant mTBI; experiencing AOC, LOC, or PTA during most significant mTBI; blast versus blunt injury type for most significant mTBI; history of any combat-related TBI; having any combat exposure or deployment-related blasts).

Examination of neurocognitive and psychiatric associations with problem drinking across groups

To provide an overall view of how veterans with mTBI history and MCs performed on neuropsychological testing, we first review the group means for the six cognitive domain *z* scores and individual subtest scores (see Table 3). We found that veterans with a history of mTBI performed below MCs on visuospatial construction, learning and memory, attention/processing speed, executive functioning, and manual motor dexterity measures. There were no group differences on the language measure. In general, both groups performed in the average range across tests, and the group differences were generally mild (typically less than one standard deviation, or 1–2 scaled score points). Notably, after including the PCL–M as a covariate (to account for the role of PTSD symptomatology), the group difference in visuospatial construction scores remained significant [i.e., Block Design; mTBI < MCs: $F(1, 57) = 4.62$, $p = .036$]. The group differences on other cognitive domain scores were no longer significant after accounting for self-reported PTSD symptoms.

Using hierarchical regression (see Table 4), we found that combat exposure (Block 1) and mTBI history (Block 2) did not account for a significant degree of variance in AUDIT scores. Adding the PCL–M score (Block 3) accounted for an additional 8% of the variance associated with AUDIT scores, although the overall model for Block 3 only approached significance. In general, a more severe level of self-reported PTSD symptoms was associated with a higher level of problem alcohol use among veterans with or without mTBI history, after accounting for combat exposure and mTBI history. The addition of the cognitive domain scores in Block 4, especially attention/processing speed (see Figure 1) and manual motor dexterity, accounted for an additional 26% of the variance in AUDIT scores above and beyond the effects of combat exposure, mTBI history, and PTSD symptoms. Higher AUDIT scores were associated with overall poorer cognitive performance. Pearson correlations are presented in Table 5 to

Table 3. Neuropsychological performance among veterans with a history of mTBI compared to MCs with no TBI history.

Neuropsychological tests and composite scores	MC (n = 27)	mTBI (n = 32)	F	p	Effect size: η^2_p
WRAT Reading SS	98.44 (18.91)	103.13 (12.71)	1.25	*ns*	.02
Executive functioning composite z-score	0.19 (0.68)	–0.15 (0.66)	3.90	* [a]	.06
D-KEFS Verbal Fluency					
Letter Fluency ss	11.67 (2.82)	10.09 (3.17)			
Category Fluency ss	12.19 (2.88)	11.38 (2.79)			
Category Fluency Switching					
Total correct responses ss	11.85 (3.07)	10.16 (3.72)			
D-KEFS Trail Making					
Number–Letter Switching ss	10.33 (2.24)	8.94 (2.99)			
WAIS Digit Span backward raw score	9.56 (2.76)	8.60 (2.27)			
Learning & memory composite z-score	0.30 (0.49)	–0.30 (0.79)	11.61	*** [a]	.17
WMS Logical Memory					
Immediate recall	11.40 (2.02)	10.31 (3.32)			
Delayed recall	10.64 (3.20)	9.93 (3.54)			
WMS Visual Reproduction					
Immediate recall	12.50 (1.68)	10.91 (2.41)			
Delayed recall	12.58 (2.66)	10.82 (3.62)			
CVLT–II					
Trials 1–5 total *t*-score	54.89 (9.38)	48.21 (8.89)			
Long delay free recall *z*-score	0.19 (1.03)	–0.63 (1.06)			
Attention & processing speed composite z-score	0.22 (0.50)	–0.22 (0.83)	5.65	* [a]	.09
WAIS–III/–IV					
Digit Span forward raw score	11.81 (2.20)	10.07 (2.64)			
Digit Symbol Coding ss	11.41 (2.41)	9.54 (2.17)			
Symbol Search ss	11.93 (2.98)	9.79 (2.55)			
D-KEFS Trail Making Test					
Visual Scanning ss	11.22 (1.91)	10.23 (3.16)			
Number Sequencing ss	11.63 (1.88)	10.58 (3.19)			
Letter Sequencing ss	11.19 (2.00)	9.94 (2.78)			
Motor Speed ss	12.00 (1.27)	11.57 (1.57)			
Visuospatial construction z-score	0.49 (0.74)	–0.43 (1.01)	15.32	*** [b]	.22
WAIS/WASI Block Design *t*-score	59.67 (5.64)	52.61 (7.75)			
Language z-score	0.16 (0.85)	–0.14 (1.11)	1.26	*ns*	.02
Boston Naming Test *t*-score	47.69 (7.88)	44.90 (10.26)			
Manual motor dexterity composite z-score	0.29 (0.69)	–0.25 (1.04)	4.94	* [a]	.09
Grooved Pegboard Test					
Dominant Hand *t*-score	51.73 (8.85)	45.63 (13.27)			
Nondominant Hand *t*-score	49.62 (8.88)	43.04 (10.74)			

Note. Values are means (and standard deviations). Participants performing below expectations on cognitive effort testing were excluded from the study. MC = military controls; mTBI = mild traumatic brain injury; ss = scaled score (mean = 10, *SD* = 3), SS = standard score (mean = 100, *SD* = 15), *t*-score (mean = 50, *SD* = 10), *z*-score (mean = 0.0, *SD* = 1.0). Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983); CVLT–II = California Verbal Learning Test–Second Edition (Delis, Kramer, Kaplan, & Ober, 2000); D-KEFS: Delis–Kaplan Executive Functioning System (Delis, Kaplan, & Kramer, 2001); Grooved Pegboard test (Lafayette Instrument, 1989); WAIS–III = Wechsler Adult Intelligence Scale–Third Edition (Wechsler, 1997a); WAIS–IV = Wechsler Adult Intelligence Scale–Fourth Edition (Wechsler, 2008); WASI = Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999); WMS = Wechsler Memory Scale–Third or Fourth Editions (Wechsler, 1997b; Wechsler, 2009); WRAT = Wide Range Achievement Test–3 or –4 (Wilkinson, 1993; Wilkinson & Robertson, 2006).

[a]Group difference is no longer significant when Posttraumatic Stress Disorder Checklist–Military Version (PCL–M) score is added as a covariate.

[b]Group difference remains significant at $p < .05$ when PCL–M score is added as a covariate.

*$p \leq .05$. ***$p < .001$. Effect sizes are presented as partial eta-squared (η^2_p, range = 0 to 1). *ns* = not statistically significant.

provide a more comprehensive view of the intercorrelations between the regression variables. As expected, many of the variables were correlated.

Discussion

In this preliminary study, we examined how problem alcohol use is associated with cognition, psychiatric functioning, combat and mTBI history, and demographic characteristics among OEF/OIF/OND veterans with or without a history of mTBI. Our analysis showed that veterans with a history of combat- or civilian-sustained mTBI reported higher levels of problematic alcohol use within the past year (28% of mTBI veterans versus 4% of MCs) and were more likely to report (a) being unable to remember what happened while drinking, or (b) that others have expressed concern about their drinking or have suggested cutting down. Aside from having a history of mTBI, high AUDIT scores (signifying problem alcohol use) were not related to any specific mTBI characteristics. However, veterans who reported AUDIT scores above the recommended clinical cutoff score were younger, had less education, and reported higher levels of PTSD, depression, and

Table 4. Four-step hierarchical multiple regression to examine associations of problem alcohol use scores (AUDIT) with combat history, mTBI history, PTSD symptoms, and cognitive performance in veterans with or without a history of mTBI.

	Step 1			*Step 2*			*Step 3*			*Step 4*		
Variable	*B*	*SE*	β	*B*	*SE*	β	*B*	*SE*	β	*B*	*SE*	β
Combat history	.13	.13	.14	.09	.14	.10	.07	.13	.08	.07	.12	.08
mTBI history				.12	.12	.15	−.05	.15	−.06	.06	.15	.08
PTSD symptoms							.008	.004	.36*	.005	.004	.20
Cognitive domain scores												
Attention/processing speed										−.22	.10	−.39*
Manual motor dexterity										−.13	.07	−.28†
Visuospatial construction										.11	.08	.25
Language										.09	.06	.22
Executive functioning										.11	.10	.19
Learning and memory										.02	.09	.03
R^2	.021			.041			.124			.383		
ΔR^2	.021			.02			.083*			.26*		
F	0.96			0.94			2.02			2.55*		

Note. AUDIT = Alcohol Use Disorders Identification Test; mTBI = mild traumatic brain injury; PTSD = posttraumatic stress disorder. AUDIT scores were log transformed prior to analysis. Combat history and mTBI history were coded as 0 = no history and 1 = positive history for combat exposure or mTBI. PTSD symptoms were measured by the PTSD Checklist–Military Version (PCL–M). Refer to text for description of cognitive domain scores.
†$p = .06$. *$p \leq .05$.

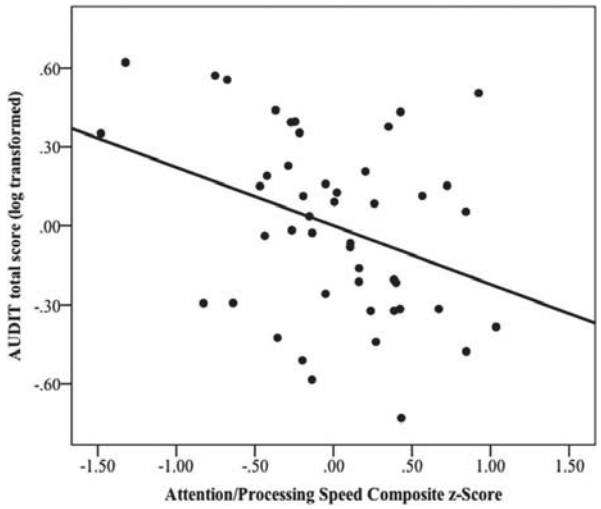

Figure 1. Partial regression plot of attention/processing speed composite *z* score and AUDIT total score (log transformed), controlling for combat exposure, mTBI history, and PTSD symptoms (PCL–M). AUDIT = Alcohol Use Disorders Identification Test; mTBI = mild traumatic brain injury; PTSD = posttraumatic stress disorder; PCL–M = PTSD Checklist–Military Version. All six cognitive domain scores were included in the hierarchical regression model. Poorer attention/processing speed was associated with higher problem alcohol use scores among veterans with or without mTBI history (β = –.39, $p = .03$).

anxiety symptoms. Although both veteran groups performed overall in the average range on cognitive testing, veterans with an mTBI history performed lower than MCs across 5/6 neuropsychological domains, including visuospatial construction, memory, attention/processing speed, executive functioning, and motor functioning. Elevated PTSD symptoms were significantly related to these cognitive differences, as only visuospatial construction scores remained significantly different between groups after controlling for self-reported PTSD symptoms. Finally, we found that higher levels of problem drinking were associated with lower attention/processing speed and motor dexterity scores, even after controlling for combat exposure, mTBI history, and PTSD symptoms.

Specifically, we examined the associations between problem alcohol use scores and cognitive performance using correlations and a four-step hierarchical multiple regression to account for combat exposure, mTBI history, and PTSD symptoms. We found that higher levels of problem drinking were associated with poorer attention/processing speed and motor dexterity in our simple correlations. Moreover, this relationship remained significant in the regression model, with overall cognitive performance accounting for about 26% of the variance in AUDIT scores after accounting for the variance associated with combat (2%), mTBI history (2%), and PTSD symptoms (8%). The other cognitive domains assessed were not specifically associated with problem alcohol use scores. Previous research in civilian mTBI populations suggests that alcohol may exert a mild, short-term negative effect on cognitive performance (Lange et al., 2007). In moderate to severe TBI patients with a history of hazardous alcohol use, Ponsford et al. (2013) found poorer memory and slowed processing speed, and more

Table 5. Pearson correlations of problem alcohol use scores, combat and mTBI history, PTSD symptoms, and cognitive domain scores among OEF/OIF/OND veterans with or without a history of mTBI.

Variable	AUDIT score	Combat history	mTBI history	PTSD symptoms	Attention/ processing speed	Motor dexterity	Executive functioning	Learning and memory	Visuospatial construction	Language
AUDIT score	—	.19	.27*	.40**	−.36**	−.40**	−.06	−.07	.004	.04
Combat history	.19	—	.31*	.25	−.18	.004	−.06	−.10	−.18	−.07
TBI history	.27*	.31*	—	.62***	−.30*	−.30*	−.25*	−.41**	−.46***	−.15
PTSD symptoms	.40**	.25	.62***	—	−.47***	−.43***	−.35**	−.44***	−.43***	−.18
Attention/ processing speed	−.36**	−.18	−.30*	−.47***	—	.22	.60***	.34**	.54***	.32*
Motor dexterity	−.40**	.004	−.30*	−.43***	.22	—	.15	.22	.08	−.007
Executive functioning	−.06	−.06	−.25	−.35**	.60***	.15	—	.39**	.39**	.30*
Memory	−.07	−.10	−.41**	−.44***	.34**	.22	.39**	—	.50***	.18
Visuospatial construction	.004	−.18	−.46***	−.43***	.54***	.08	.39**	.50***	—	.13
Language	.04	−.07	−.15	−.18	.32*	−.007	.30*	.18	.13	—

Note. AUDIT = Alcohol Use Disorders Identification Test; mTBI = mild traumatic brain injury; OEF/OIF/OND = Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn; PTSD = posttraumatic stress disorder. AUDIT scores were log transformed prior to analysis. Combat history and mTBI history were coded as 0 = no history and 1 = positive history for combat exposure or mTBI. PTSD symptoms were measured by the PTSD Checklist–Military Version (PCL–M). Refer to text for description of cognitive domain scores.
*$p < .05$. **$p < .01$. ***$p < .001$.

recent alcohol use had a particular effect on executive functioning. We believe our preliminary study may be the first to report a relationship between past year problem alcohol use and poorer attention/processing speed in a sample of veterans with or without a history of mTBI, while also accounting for the influence combat, mTBI, and PTSD symptoms.

In non-TBI civilian populations, long-term heavy alcohol use has been associated with a variety of cognitive deficits. Specifically, during the acute detoxification period, general cognitive impairment is common (Fein et al., 1990), including decrements in visuospatial, memory, and executive functions (Reed, Grant, & Rourke, 1992; Sher, Martin, Wood, & Rutledge, 1997; Sullivan, Rosenbloom, & Pfefferbaum, 2000). Attention/concentration, reaction time, and memory may improve following several weeks of abstinence (Bates et al., 2005; Fein et al., 1990); however, executive functions, processing speed, and visuospatial skills may remain affected (Bates et al., 2005; Fein et al., 1990). Adults appear to recover most neurocognitive abilities following several years of abstinence (Reed et al., 1992), but visuospatial skills may be less likely to fully recover (Fein et al., 2006). Factors that can influence the extent of neurocognitive recovery include age, premorbid cognitive ability, length of abstinence, and amount of drinking in the intervening time (Bates et al., 2005; Fein et al., 1990; Rourke & Grant, 1999). In military or veteran populations, history of TBI, combat, deployment, and PTSD and other psychiatric symptoms should also be considered.

Aside from the alcohol-related differences, we found that, overall, veterans with mTBI history had poorer performance across several neuropsychological domains than veterans who did not experience a TBI event, such as in processing speed (Frencham et al., 2005; Levin et al., 2013), attention, learning/memory (Mathias et al., 2004; Sozda et al., 2014), and executive functioning (Demery, Larson, Dixit, Bauer, & Perlstein, 2010; Sorg et al., 2014). Overall, these group differences were mild (e.g., one to two scaled score points), and both groups primarily performed in the average range. Nevertheless, others did not report lasting cognitive decrements in veterans with a history of head trauma (Ivins, Kane, & Schwab, 2009), unless they had a comorbid psychiatric condition (Nelson et al., 2012). Consistent with previous research (Adams, Corrigan, et al., 2012; Taylor et al., 2012), veterans with mTBI history in the current sample reported more significant psychiatric symptoms on self-report questionnaires assessing depression, anxiety, and PTSD symptoms than MCs. We found that, after controlling for self-reported PTSD symptoms, the groups still differed on a measure of visuospatial construction but not on the other domains.

Indeed, individuals sustaining a combat-related TBI (69% of mTBI veterans in the current study)

are at risk for both the physical and psychiatric effects of such trauma (e.g., Lew, Otis, Tun, Kerns, Clark, & Cifu, 2009). Several studies have noted the many overlapping symptoms of mTBI and PTSD that make the assessment and treatment of both disorders challenging, such as depression, anxiety, poor sleep, fatigue, and difficulty concentrating (e.g., Adams, Corrigan, et al., 2012; Brady et al., 2009; Stein & McAllister, 2009). Our findings further emphasize that PTSD or other psychiatric symptoms may play a role in poorer cognitive performance but that there may be some persisting cognitive changes following mTBI above and beyond psychiatric symptoms. Notably, the current study (a) examined for the role of psychiatric symptoms in cognitive test scores, and (b) excluded participants who performed below expectations on cognitive effort testing. Differences in participant populations, measures, and analyses may explain contrasting results between studies.

Our findings regarding alcohol use among veterans with mTBI are consistent with previous research that has shown an increased risk of binge drinking or alcohol dependence among military personnel with a history of TBI (Adams, Larson, et al., 2012; Heltemes et al., 2011; Miller et al., 2013). However, we note that problem alcohol use has been identified as a risk factor for sustaining a head injury in civilian settings, and that individuals who misuse alcohol prior to injury may be more likely to continue or increase drinking following a TBI (see review by Bjork & Grant, 2009). In the current study, we were not able to examine preinjury alcohol use, and we did not include individuals who met clinical criteria for current alcohol abuse or lifetime history of alcohol dependence. Therefore, this study examined a range of primarily nonclinical alcohol use among veterans with and without a history of mTBI, and additional research is needed to examine whether mTBI, itself, increases risk for heavy alcohol use.

Consistent with previous research (e.g., Jacobson et al., 2008; Schumm & Chard, 2012; Stahre et al., 2009), veterans reporting higher levels of problem drinking tended to be several years younger in age (on average, 27 years old ± 4 years versus 33 years old ± 8 years) and have less education (on average, 13 years ± 1 versus 15 years ± 2). However, earlier studies also reported that White or Hispanic ethnicity, male gender, greater combat exposure, and military branch of service (Marines or Army) were associated with more problematic alcohol use. In the current study, we did not find the latter associations among veterans with mTBI, and, notably, problem alcohol use was *not* associated with specific mTBI characteristics (e.g., number of mTBI events, LOC, PTA, type or circumstances of injury). Veterans with higher levels of problem drinking also reported, on average, clinically significant levels of PTSD symptoms and moderate levels of depression and anxiety. Green, Bekham, Youssef, and Ebogen (2014) reported similar findings in a U.S. military sample (TBI not assessed). Specifically, they found that lower "psychological resilience" (after accounting for demographic factors, combat history, and probable PTSD) was associated with greater alcohol misuse. Again, methodological differences may explain varying findings between studies, but we suggest that greater psychiatric concerns (PTSD, depression, anxiety), poorer attention/psychomotor processing speed, and lower age and education were most strongly associated with past-year alcohol-related problems assessed with a brief, self-report, alcohol screening questionnaire.

Strengths limitations, and future directions

To our knowledge, this is the first study that has investigated the relationship between alcohol use, cognition, and psychiatric functioning within a military/veteran mTBI population. We also incorporated a demographically similar veteran control group for comparison on cognitive and psychiatric measures, used a data reduction technique with our neuropsychological measures to reduce the possibility of Type I error, and excluded participants who did not meet minimum requirements on effort testing during the neuropsychological battery. However, there are important limitations of the current study that should be noted. For example, although we found no group differences with respect to mechanism of injury, our TBI group was heterogeneous (composed of both combat- and civilian-sustained TBIs), and there may be different sequelae given the additional possible trauma and stresses of deployment and combat situations. While we were able to examine whether having any combat exposure was related to AUDIT scores, we did not have data regarding the number of times deployed or the number/degree of combat situations. Additionally, we did not exclude participants with current psychotropic or pain medication use given that such exclusion would have resulted in a very small and nonrepresentative sample size. Further, we recruited veterans from VA

clinics, research studies, and surrounding communities; thus, our sample is relatively diverse but represents only a subset of OEF/OIF/OND and Persian Gulf veterans with or without mTBI histories. Additional research is needed to (a) examine alcohol use and cognition in other specific veteran groups or an even wider diversity of veterans and (b) study the influence of the number of deployments, degree of combat exposure, medication use, and other important variables.

We would like to note that participants were not selected for their alcohol use characteristics, and those with current (within 30 days) DSM–IV alcohol/other substance abuse or lifetime dependence history were excluded. Therefore, this sample generally represents veterans with a range of "typical" alcohol use, rather than "clinical" alcohol use. It is possible that a sample of heavier alcohol users would show stronger relationships between alcohol use, psychiatric symptoms, cognition, and other variables examined within this study. Because those with a history of mild neurotrauma have been difficult to distinguish from patients in treatment for substance use disorders (Lange et al., 2008), inclusion of a group of veterans with recent or past substance use/abuse disorder with and without TBI history may be informative. Alcohol use was not comprehensively assessed prior to sustaining head trauma, and the average time since their most significant mTBI at this assessment was approximately four years. Therefore, the natural history of lifetime alcohol use was not monitored, and changes relating to mTBI or other trauma(s) were not directly assessed. Future studies that track the interplay of mTBI, alcohol use, psychiatric functioning, and cognition over time would enhance our understanding of how alcohol use is influenced by TBI and, in turn, how problem alcohol use affects other important areas of functioning. Finally, given previous work that has shown (a) sensitivity in brain response to alcohol following TBI (e.g., Lowing et al., 2014) and (b) associations between substance abuse, TBI, and atrophic changes on quantitative magnetic resonance imaging (MRI; Barker et al., 1999; Bigler et al., 1996), further research examining brain changes associated with cognitive and psychiatric symptomatology in mTBI samples is needed.

Conclusions and clinical implications

In summary, we found that (a) veterans with a history of mTBI reported more past-year alcohol-related problems than non-TBI military controls (e.g., not recalling events that occurred while drinking, others suggesting they cut down); (b) elevated problem alcohol use scores were most strongly associated with more severe psychiatric symptoms, younger age, and less education (but *not* specific mTBI characteristics, combat exposure, or other demographic variables); and (c) poorer attention and psychomotor processing speed were associated with higher levels of self-reported problem alcohol use, even after accounting for history of combat exposure, mTBI, and PTSD symptoms. Taken together, our findings emphasize the importance of assessing for and treating problematic alcohol use among veterans, including those with a history of neurotrauma given the increased risk for a variety of likely interacting issues. This may help reduce possible adverse consequences in the military/veteran population, including poor recovery from post-traumatic stress, work-related problems, legal issues, additional injuries, and engaging in risk-behaviors (e.g., driving while intoxicated, getting into fights, having unprotected sex; see Adams, Corrigan, et al., 2012; Schumm & Chard, 2012; Stahre et al., 2009).

In terms of treatment implications, a mildly slower processing speed may be expected among veterans with problem alcohol use. Therefore, a slower approach in therapy and attempting one task at a time may be important considerations. Considering our findings in concert with previous research, clinicians working with veterans who have a history of TBI, especially recent TBI, may recommend a reduction or abstinence from alcohol to help veterans avoid additional injury and improve or maintain their overall cognitive and psychiatric functioning. Although research is still developing on the best practices for treatment of comorbid psychiatric and alcohol-related problems in veteran populations, an integrated approach that considers both psychiatric issues (e.g., PTSD, depression, anxiety) and alcohol misuse (as well as mTBI history) may be most beneficial (see Adams, Corrigan, et al., 2012).

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No conflicts of interest were declared.

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White Matter Associations With Performance Validity Testing in Veterans With Mild Traumatic Brain Injury: The Utility of Biomarkers in Complicated Assessment

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Objective: Failure on performance validity tests (PVTs) is common in Veterans with histories of mild traumatic brain injury (mTBI), leading to questionable validity of clinical presentations. **Participants:** Using diffusion tensor imaging, we investigated white matter (WM) integrity and cognition in 79 Veterans with history of mTBI who passed PVTs ($n = 43$; traumatic brain injury [TBI]-passed), history of mTBI who failed at least 1 PVT ($n = 13$; TBI-failed), and military controls ($n = 23$; MCs) with no history of TBI. **Results:** The TBI-failed group demonstrated significantly lower cognitive scores relative to MCs and the TBI-passed group; however, no such differences were observed between MCs and the TBI-passed group. On a global measure of WM integrity (ie, WM burden), the TBI-failed group showed more overall WM abnormalities than the other groups. However, no differences were observed between the MCs and TBI-passed group on WM burden. Interestingly, regional WM analyses revealed abnormalities in the anterior internal capsule and cingulum of both TBI subgroups relative to MCs. Moreover, compared with the TBI-passed group, the TBI-failed group demonstrated significantly decreased WM integrity in the corpus callosum. **Conclusions:** Findings revealed that, within our sample, WM abnormalities are evident in those who fail PVTs. This study adds to the burgeoning PVT literature by suggesting that poor PVT performance does not negate the possibility of underlying WM abnormalities in military personnel with history of mTBI. **Key words:** *diffusion tensor imaging*, *effort testing*, *mild traumatic brain injury*, *performance validity*, *white matter*

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INVALID PRESENTATION of cognitive functioning during neuropsychological assessment limits clinical inferences and complicates diagnostic decision making. Performance validity tests (PVTs) have been utilized in examinations of Veterans with mild traumatic brain injury (mTBI) to provide objective measurement of whether observed cognitive test performances are

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valid and reliable. Failure on PVT measures has been associated with decreased cognitive test performance, evaluation context, and increased endorsement on postconcussion symptom checklists.[1–9] The utility of PVTs in clinical populations has primarily been demonstrated by the failure to establish an association between poor PVT performance and bona fide clinical syndromes.[10–12] The ease of the PVT task is such that even individuals with significant neurological deficits typically pass PVTs,[13,14] indicating that poor PVT performance is generally not a consequence of cognitive impairment. This insensitivity to cognitive impairment is further shown within traumatic brain injury (TBI) as those with more severe injuries demonstrate lower rates of poor PVT performance when compared with those with milder injuries.[15–17] As such, PVT failure has largely been interpreted as a nonneurological factor that obscures the investigation of residual symptoms and cognition in Veteran mTBI samples.

The vast majority of research examining the role of PVTs in the context of a clinical evaluation has occurred in forensic settings where external incentives are salient.[18,19] In such settings, external financial or legal gain has been implicated as the source for PVT failure. However, in nonforensic settings, where there is less obvious motivation for secondary gain, why poor PVT failure occurs is less clear. Proposed explanations outside of direct monetary incentives include attempts to gain access to clinical care, overly focus on or exaggerate genuine deficits, adoption of social psychological factors (eg, illness perception and diagnosis threat), and iatrogenic consequences.[20–24] However, such explanations are largely speculative, and despite the increasing study of PVT performance in Veterans,[1–3,5,6–9] the clinical presentations of those who fail PVTs remain poorly understood.

Although poor PVT performance alerts examiners to potentially invalid cognitive test performance and patterns of exaggerated symptom reporting, invalid test results do not negate the possibility of brain damage or genuine cognitive impairment[25–28]; thus, non–performance-based biomarkers of neurotrauma (eg, imaging findings) may therefore prove useful in determining the presence of damage that may be related to the reported symptoms and clinical outcome. For example, a recent study examined magnetic resonance spectroscopic metabolites in a sample of Veterans with self-reported memory impairment and history of blast-related TBI to investigate correlates of brain alterations.[28] Results of this study showed that those who failed PVTs demonstrated magnetic resonance spectroscopic metabolite values roughly 1.5 to 2 standard deviations below the mean of control participants in the hippocampus, suggesting that a biological correlate of neural impairment was present, even in those who failed PVTs.

Clarifying whether underlying brain abnormalities are present among those failing PVTs is an important clinical issue, especially in Veterans' health settings, where TBI is regarded as the signature injury of the wars in Iraq and Afghanistan.[29] Therefore, using diffusion tensor imaging (DTI), we investigated cerebral white matter (WM) microstructure of Veterans with reported histories of head injury and compared them to a military control (MC) sample without history of TBI. Our mTBI sample was subdivided into 2 groups on the basis of performances above or below recommended cut-points on PVTs. We hypothesized that, although cognitive test performance would be significantly reduced in the TBI-failed group relative to the other 2 groups, the TBI-failed group would consist of a mixed sample of those with and without WM microstructural damage; thus, their level of WM damage was expected to fall between MC and PVT-passed groups.

METHODS

Participants

Study participants were 79 (TBI: $n = 56$, MCs: $n = 23$) Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn (OEF/OIF/OND) service members who were recruited from the VA San Diego Healthcare System (VASDHS) and the University of California, San Diego (UCSD) via word-of-mouth, posted recruitment fliers, and referrals from the VASDHS TBI Clinic. Only participants with mTBI were included in the study, and of the TBI participants $n = 43$ passed PVT measures (TBI-passed), whereas $n = 13$ failed (TBI-failed). Study participants received comprehensive neuropsychological testing and magnetic resonance scanning (MRI) scanning, as well as administration of self-report measures of psychiatric symptomatology. All participants provided written and informed consent in compliance with the institutional review boards of the VASDHS and the UCSD.

The following exclusionary criteria were applied to the study sample–(1) failure to complete PVT testing; (2) moderate or severe TBI; (3) current or past history of a significant neurological condition (eg, seizures and multiple sclerosis); (4) current or past serious medical illness (eg, cerebrovascular accident and myocardial infarction); (5) hearing or vision impairment that interfered with neuropsychological performance; (6) lack of English proficiency; (7) current psychiatric illnesses that are likely to impact brain morphometry and/or neuroendocrine functioning (eg, schizophrenia and bipolar disorder); (8) current substance/alcohol abuse or dependence as indicated by concordance with the *Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)* criteria; (9) any contraindications to MRI (eg, shrapnel and ferromagnetic implants); and (10) involvement in current or pending litigation.

TBI diagnostic procedure

Diagnosis of mTBI was based on Department of Defense and VA TBI Task Force guidelines for mTBI[30]–(1) Glasgow Coma Scale (when available) score of 13 to 15; (2) presence and duration of loss of consciousness (LOC) of 30 minutes or less; (3) presence and duration of alteration of consciousness (AOC) of 24 hours or less; and/or (4) presence and duration of posttraumatic amnesia (PTA) of 24 hours or less. All participants were assessed for nonmilitary (prior to or after discharge from the military) and military-related head injuries. Military-related injuries were assessed separately for blast and blunt mechanisms of injury. With respect to blasts, participants were also asked to estimate total number of blast exposures, distance, and the direction from which the blast was initiated (ie, front, back, left, and right).

Traumatic brain injury relevant information was obtained via open-ended questioning and prompts via a laboratory-based questionnaire modeled on the VA's semistructured clinical interview for TBI identification.[31] This measure was developed specifically to address the aims of the broader TBI study and at present lacks the rigorous psychometric evaluation of more established clinical interviews[31–33] and screening measures[34–36] for TBI. However, this measure is similar to other available instruments in that it addresses several key aspects of traumatic events including the number of head injuries sustained, important diagnostic data for each (eg, duration of LOC, AOC, and PTA), and the mode of injury (ie, blast or blunt force). Specifically, participants are asked to recall in detail any falls, fights, blast exposures, sporting events, or any other experiences in which they may have hit or suffered a blow to their head. A trained interviewer probed for details about diagnostic criteria (ie, LOC, AOC, and PTA) and collected information with respect to whether injuries occurred in combat, medical attention was received, and about the presence and persistence of neurological symptoms (ie, nausea, headaches, fatigue, and blurry vision) after each reported injury.

Neuropsychological assessment

Participants completed a neuropsychological test battery that included (1) Trail Making and Verbal Fluency tests of the Delis Kaplan Executive Function System (D-KEFS)[37]; (2) California Verbal Learning Test-Second Edition (CVLT-II)[38]; (3) Wisconsin Card Sorting Task-64 Card Version (WCST-64)[39]; and (4) reading subtest of the Wide Range Achievement Test-Fourth Edition (WRAT-4).[40] Participants also completed self-report measures including the Neurobehavioral Symptom Inventory[41]; Posttraumatic stress disorder Checklist (PCL-M)[42]; and Beck-Depression Inventory-II (BDI-II).[43] Because of its later inclusion in the larger study, Neurobehavioral Symptom Inventory data were available for only 45 TBI participants (TBI-passed: $n = 36$, TBI-Failed: $n = 9$).

Assessments of performance validity

The Test of Memory Malingering (TOMM) is a stand-alone PVT designed to detect inadequate test motivation[14] and is especially sensitive and specific to detecting inadequate test engagement in head-trauma samples.[44,45] Similarly, the CVLT-II Forced Choice Recognition (CVLT-FCR) is a brief, embedded measure of performance validity that has been validated in TBI samples.[45] Invalid test performance was determined by a TOMM Trial 2 score of less than 45 or CVLT-FCR less than 15.[14,45]

Neuroimaging protocols, processing, and analysis

All participants underwent structural MRI and DTI on a 3 Telsa General Electric MRI using the MR750 platform at the UCSD Functional Magnetic Resonance Imaging Center. A radiologic technician with expertise in neuroimaging processing and analysis reviewed all structural scans for lesions.

Structural scanning

A sagittally acquired high-resolution 3D T1-weighted anatomical MRI was collected with the following parameters: Field of view (FOV) = 24 cm, 256 × 256 × 192 matrix, 0.94 × 0.94 × 1 mm voxels, 176 slices, TR (Repetition Time) = 20 ms, TE (Echo Time) = 4.8 ms, flip angle = 12°, over approximately 7 minutes.

Diffusion tensor imaging

All DTI images were collected via dual spin echo EPI acquisition.[46] The b = 0 was used for anatomical reference. Diffusion tensor imaging scan parameters were–FOV = 240 mm, slick thickness = 3 mm, matrix size = 128 × 128, in-plane resolution = 1.875 × 1.875, TR = 8000 ms, TE = 93 ms. Thirty-four slices were acquired with 61 diffusion directions distributed on the surface of a sphere in conjunction with the electrostatic repulsion model[47] and a b value of 1500 s/mm^2, in addition to 1 T2 weighted image with no diffusion ($\beta = 0$). Distortions due to magnetic field heterogeneity were corrected with 2 field maps with identical spatial parameters as those of collected DTI scans. Total scan time for DTI acquisition and field mapping was approximately 12 to 16 minutes.

Diffusion tensor imaging was used for in vivo quantification of the direction and magnitude of water molecules within WM.[48] Fractional anisotropy (FA) is a directional measure of diffusion ranging from 0

(isotropic diffusion) to 1 (perfectly anisotropic diffusion) that is reflective of fiber integrity.[49–52] Subsequent DTI parameters are obtained through diagonalization, and resulting eigenvalues provide further information about WM microstructures.[48,52] Specifically, axial diffusivity (AD), defined by the principal eigenvalue (ie, AD = $\lambda 1$), reflects the degree of diffusion parallel to axon fibers.[51,53] Decreased AD has been shown to be reflective of axonal injury in ischemic WM lesions.[54] Radial diffusivity (RD) was defined as the average of the second and third eigenvalues (ie, RD = $(\lambda 2 + \lambda 3)/2$) and is a measure of diffusivity perpendicular to axonal fibers.[49,53] Increased RD has been linked to demyelination after traumatic injury.[53]

DTI processing

Diffusion tensor imaging processing was performed utilizing the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Library (FSL).[55] Two field maps were utilized to unwrap EPI acquisitions, and all images were corrected for motion artifact using the eddy correct FSL command. Visual inspection of all images was performed for quality assurance, and the FSL *bet* command was utilized to remove nonbrain voxels from analyses. The FSL program *ditfit* framed a diffusion tensor model to each voxel to generate the DTI index of FA and corresponding eigenvalues on a voxel-by-voxel basis.

Tractography

Using the Fiber Assignment by Continuous Tracking method,[56] fiber tracts were generated in TrackVis Massachusetts General Hospital (MGH) according to "seed points" placed in regions of interest (ROIs). This occurred via bilateral seed point placement within the following WM tracts: anterior and posterior limbs of the internal capsule (IC); genu, body, and splenium of the corpus callosum (CC); the fornix; and cingulum bundle. A blind rater placed seed ROIs in every subject's color-map image in TrackVis. A color-coded scheme, seen by loading the principle eigenvector image in FSL, was generated to display each voxel's main orientation of diffusion. This information, in conjunction with a nondiffusion weighted map, allowed the rater to delineate seed point ROIs for fiber tracking. A mean FA, AD, and RD value was extracted from the length of each track and utilized for composition of our main outcomes measures of white matter burden (WMB). The reduction of partial voluming effects due to encroaching gray matter was achieved by the inclusion of voxels with FA values greater than 0.20,[57] and irregular tracking was restricted by the implementation of an angle threshold of 41.4°.[58]

Region of interest seeding

Internal capsule

Diffusion tensor imaging segmentation of the IC followed Wakana and Jiang' procedures.[59] The ROI placement for the anterior IC occurred within green-colored voxels (see Figure 1), and ROI seeds were placed in the axial plane between the putamen and caudate. The ROI placement for the posterior IC occurred within blue-colored voxels, and ROI seeds were placed medial to the lenticular nucleus (pallidum and putamen) and lateral to the thalamus.

Corpus callosum

The entire CC was tracked by ROI seed placement within red-colored voxels in a mid-sagittal slice of known CC anatomy utilizing Wakana and Jiang procedures.[59] Subdivisions of the CC (eg, genu, body, and splenium) were identified using an adapted fiber tracking method.[60]

Cingulum

Placement occurred within green-colored voxels inferior to the cingulum gyrus and superior to the CC in the coronal plane. Distinct ROIs were placed for the anterior, middle, and posterior aspects of the cingulum following Concha et al methodology.[61]

Fornix

Per Concha and colleagues,[61] ROI placements occurred in the body, crus, and column.

Total WM burden

Overall WMB, an index of global WM integrity, was calculated to capture the number of ROIs with compromised WM integrity (see 62). This measure reduces individual variability due to the heterogeneous nature of TBI, has been demonstrated to distinguish TBI participants from controls, and is more tightly associated with reduced cognition relative to DTI-derived ROI indices.[62] First, *z* scores were calculated for the 10 ROIs across each DTI index using the MCs' means and standard deviations. Next, WMB was calculated by summing the total number of ROIs greater than 1 standard deviation *below* the control mean for FA and AD, separately. As increased RD may be indicative of membrane permeability or demyelination,[53] WMB for RD was calculated by summing the total number of ROIs greater than 1 standard deviation *above* the control mean. In all, 3 WMB variables were generated for each DTI index and total WMB loads ranged from 0 to 10. Higher WMB (eg, 10) is indicative of a greater number of ROIs that displayed values below (for FA and AD) or above

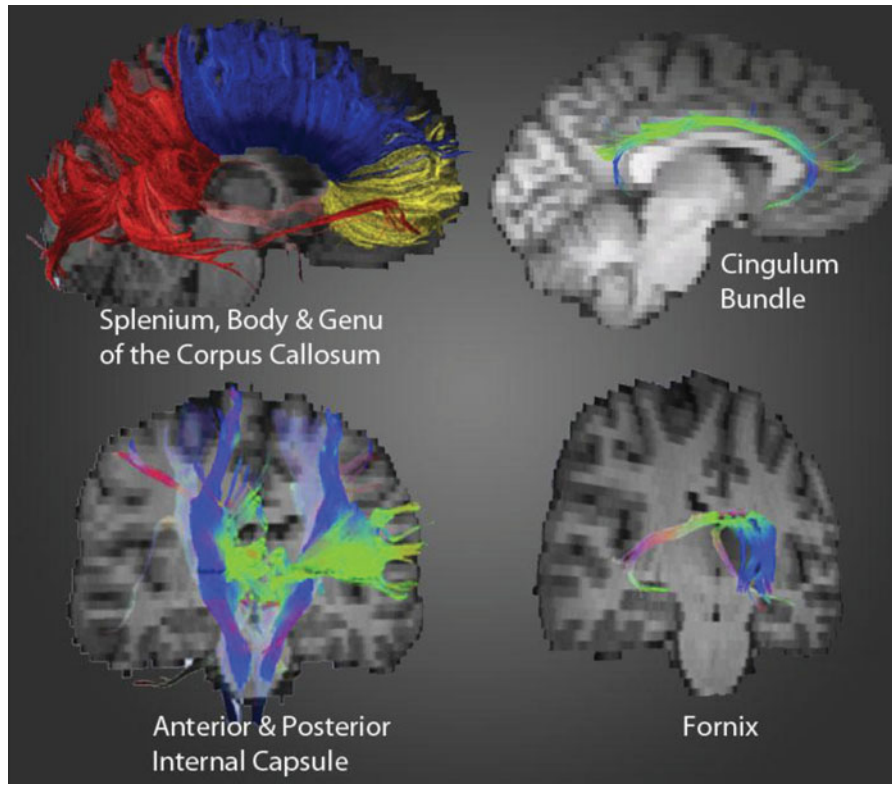


Figure 1. Fiber tracks of interest.

(for RD) the control means and is representative of *worse* overall WM integrity.

Statistical analyses

Formal group comparisons for all categorical data utilized the chi-square analyses. For continuous data, the Shapiro-Wilk test was conducted to determine whether the assumption of normality was met, whereas the Levene test was utilized to determine whether there were homogeneous variances between the groups. For quantitative data, outlier analyses were conducted using Hoaglin and Iglewicz[63] recommendations, which are more sensitive and appropriate for nonnormal distributions and small-to-moderate sample sizes.[63,64] Group comparisons for continuous data were conducted using the 1-way analysis of variance (ANOVA) tests, followed by planned contrast testing (*t* tests). For WMB and neuropsychological variables, multiple comparison corrections were conducted using the Tukey Honestly Significant Differences. The Dunnett T3 was used for multiple comparisons when there were heterogeneous variances between the groups and multiple comparisons were not performed for group comparisons of WM ROIs due to the exploratory nature of these analyses. The Kruskal-Wallis test was conducted to verify any findings in which the assumption of normality was violated. All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 21 (SPSS IBM, New York, New York).[65]

RESULTS

PVT performance

No MCs performed below PVT cutoff scores. Of those with TBI, 43 passed both PVTs (TBI-passed) and 13 failed at least 1 PVT (TBI-failed) reflected as obtaining a score below published cutoffs on either test. Within the TBI-failed subgroup, 9 individuals (69.2%) scored below threshold on the CVLT-FCR, 3 scored below threshold on only the TOMM (23.1%), and 1 individual (7.7%) scored below threshold on both measures. There were no individuals who scored below chance on the CVLT-FCR or the TOMM. This overall rate of poor PVT performance within the sample (16%) is commensurate with previously reported PVT failure rates in Veteran mTBI samples within a research context.[7]

Participant demographic and clinical characteristics

Participant demographics, injury characteristics, and self-reported symptom rating scales are presented in Table 1. The groups did not significantly differ with respect to age or sex (all $P > .10$); however, ANOVA revealed significant differences with respect to years of education ($P = .02$). Both the TBI-passed and TBI-failed

TABLE 1 *Participant characteristics, mean (standard deviation)*

N	Military Controls 23	TBI-passed 43	TBI-failed 13	*P*
Age, y	32.9 (7.9)	32.9 (8.2)	31.5 (8.5)	.86
[a]Sex (men:women)	16:7	38:5	12:1	.11
[a]Ethnicity				
Caucasian	19	17	9	<.001
African American	1	5	0	
Hispanic	0	16	1	
Asian	0	2	3	
Other	3	3	0	
Years of education	15.1 (2.0)	14.1 (1.6)	13.5 (1.9)	.02
WRAT Reading Standard Score	101.3 (16.9)	99.4 (14.4)	98.9 (8.0)	.85
Number of mTBIs	...	2.4 (1.3)	3.2 (2.0)	.11
[a]% Reporting blast exposure	...	69.8%	69.2%	.97
Self-reported blast exposures	...	4.1 (12.92)	4.8 (7.0)	.85
[a]% Reporting any LOC	...	53.5%	76.9%	.12
"Worst" TBI LOC duration in minutes	...	6.08 (9.3)	7.25 (7.0)	.75
Months since last TBI	...	64.4 (43.8)	34.0 (20.3)	.02
NSI Total Score	...	32.7 (17.4)	48.8 (10.8)	.01
BDI-II Total Score	3.0 (4.3)	19.1 (11.1)	28.3 (13.3)	<.001
PCL-M Total Score	19.9 (4.1)	43.6 (17.0)	63.8 (10.4)	<.001

Abbreviations: BDI-II, Beck Depression Inventory-II; PCL-M, Posttraumatic Stress Disorder Symptom Checklist-Military; LOC, loss of consciousness; NSI, Neurobehavioral Symptom Inventory; TBI, traumatic brain injury; WRAT, Wide Range Achievement Test-4.
[a]Likelihood ratio utilized.

subgroups demonstrated significantly fewer years of education than the MC group ($P = .03$, $P = .01$, respectively), yet there were no differences in years of education between the TBI-passed and TBI-failed subgroups. There were no group differences with respect to estimated premorbid verbal ability (WRAT reading, $P > .10$). However, the chi-square analysis revealed the groups significantly differed with respect to ethnicity ($P = .001$), with the TBI-passed subgroup comprised more Hispanic individuals compared with the MCs and the TBI-failed group.

Analysis of variances revealed that the TBI-passed and TBI-failed subgroups did not differ in percentage of individuals with blast exposure, the number of self-reported blast events, or most TBI characteristics (all $P >$ .10). The last TBI event for the TBI-failed subgroup was closer in time to the date of assessment than the TBI-passed group ($P = .02$). The groups significantly differed in terms of self-reported psychiatric and neurological symptoms (all $P < .001$). Both the TBI-passed and TBI-failed subgroups showed significantly greater BDI and PCL scores (all Ps $< .001$) when compared with MCs. The TBI-failed subgroup endorsed significantly greater psychiatric and neurobehavioral symptoms when compared with the TBI-passed subgroup (all $P < .05$).

Exploration of WMB indices

One-way ANOVAs were used to examine whether there were group differences on WMB. The independent variable utilized in each analysis represented the 3 groups–MCs, TBI-passed, and TBI-failed. The dependent variables were WMB indices of FA, RD, and AD. See Table 2 for means, standard deviations, and

TABLE 2 *White matter burden by group*

DTI index of WMB	Military Controls Mean (SD)	TBI-passed Mean (SD)	TBI-failed Mean (SD)	*P*[a] MCs vs TBI-passed	MCs vs TBI-failed	TBI-passed vs TBI-failed
FA WMB	1.30 (1.77)	1.77 (2.12)	3.69 (2.92)	0.69	**0.01**	**0.02**
RD WMB	1.56 (2.59)	2.28 (2.36)	2.46 (2.50)	0.16	0.24	0.97
AD WMB	0.45 (0.85)	0.73 (1.31)	1.69 (2.02)	0.65	0.14	0.33

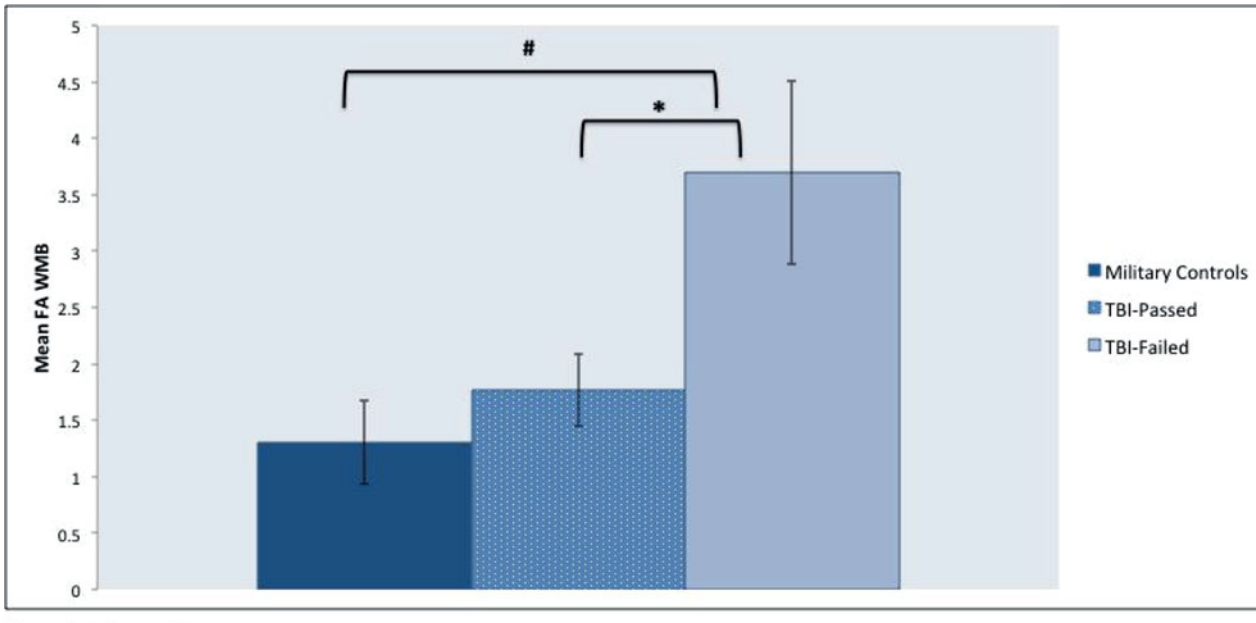
Abbreviations: AD, axial diffusivity; DTI, diffusion tensor imaging; FA, fractional anisotropy; MCs, military controls; RD, radial diffusivity; SD, standard deviation; TBI, traumatic brain injury; WMB, white matter burden.
[a]Bolded *P* values indicate a value less than .05 ($P < .05$) and are significant.

significance levels. With respect to FA-WMB, outlier analyses revealed that there were no extreme values across any of the groups. The Shapiro-Wilk test demonstrated that the fundamental assumption of normality was violated across both the MCs and TBI-passed groups (all *P*s < .001), but not the TBI-failed group ($P = .328$). Visual inspection of the distributions for each group showed positively skewed distributions for the MCs and TBI-passed group, whereas the distributions for the TBI-failed group appeared relatively uniform in shape. In addition, the Levene test of homogeneity of variances was not significant ($F_{2,76} = 2.319$, $P = .105$), indicating this underlying assumption was met and outlier analyses revealed no extreme values.

Analysis of variance showed a statistically significant main effect of group ($F_{2,76} = 5.310$, $P = .007$, $\eta^2_p = 0.12$), for FA-WMB. Follow-up contrasts demonstrated that the TBI-failed subgroup had significantly greater FA-WMB (more ROIs differed from that of controls) than both the MC (Cohen $d = 1.08$, $P = .006$) and TBI-passed (Cohen $d = 0.83$, $P = .018$) groups (see Figure 2). However, no significant differences were observed between MCs and the TBI-passed groups ($P > .50$). Although the 1-way ANOVA is generally robust against violations of nonnormality,[66] nonparametric statistics were used to verify findings. The Kruskal-Wallis test revealed that there was a statistically significant difference between the groups on FA-WMB (χ^2 (2) = 7.647, $P = .022$) with a mean rank of 34.22 for the MCs, 38.58 for the TBI-passed group, and 54.92 for the TBI-failed group. Post hoc analyses of the Kruskal-Wallis test revealed similar differences between the groups; that is, mean ranks for TBI-failed group were statistically significant from both the TBI-passed ($P = .020$) and MC ($P = .007$) groups, but there were no significant differences ($P = .446$) between the MCs and TBI-passed groups.

With respect to RD-WMB, the Shapiro-Wilk tests revealed that the distributions of all groups were not normally distributed (*P*s < .05). Visual inspection of the distributions for each group showed positively skewed distributions for the MCs and TBI-passed group, whereas the distribution for the TBI-failed group appeared relatively uniform in shape. Outlier analyses revealed that there was an outlier (MCs group; value of 10), which was removed prior to conducting subsequent analyses. The Levene test demonstrated that the fundamental assumption of homogeneous variances was met ($F_{2,75} = 1.241$, $P = .295$). Inspection of the group means for the RD-WMB showed a WMB pattern similar to that of FA-WMB (MCs < TBI-passed < TBI-failed). However, ANOVA revealed that there was no main effect of group ($F_{2,75} = 2.040$, $P = .137$), nor did follow-up contrasts reveal any significant differences between the groups (all *P*s > .05). The Kruskal-Wallis test revealed that there were no significant differences between the groups on RD-WMB (χ^2 (2) = 5.014, $P = .082$) as well.

With respect to AD-WMB, the Shapiro-Wilk tests revealed that the fundamental assumption of normality was violated across all groups (all *P*s < .005). Visual inspection of the distributions for each group showed positively skewed distributions for the MCs and TBI-passed group, whereas the distributions for the TBI-failed group appeared relatively uniform in shape. Outlier analyses



$p = .01$, * $p = .02$. Errors bars = standard error of mean.

Figure 2. Fractional anisotropic index of white matter burden by group.

revealed 2 outliers (MCs group, value of 10; TBI-passed group, value of 7), which were removed prior to conducting the group analyses. The Levene test revealed that the groups for heterogeneous variances was not met ($F_{2,74} = 5.941$, $P = .004$); therefore, group differences were examined via the more appropriate Welch ANOVA.[67] The Welch ANOVA is especially robust to both violations of normality and heterogeneous variances.[67–69] Inspection of the group means for the AD-WMB showed a pattern similar to that of the other WMB indices (MCs < TBI-passed < TBI-failed). However, results revealed no main effect of group ($F_{2,28.546}) = 2.348$, $P = .114$), nor follow-up contrasts revealed that there were any significant differences between the groups (all Ps > .05). The Kruskal-Wallis test was not conducted for AD-WMB, as this test is not robust to heterogeneous variances.[70]

Exploration of WM ROIs

Analysis of variances were conducted to examine differences across WM ROIs (see Table 3). There were some violations of normality and heterogeneity across the groups; however, when the Kruskal-Wallis tests were conducted for variables with nonnormal distributions, the results did not differ from ANOVA results. Outlier analyses revealed no extreme values.

In regard to FA, there was a main effect of group for the left cingulum ($\eta^2_p = 0.09$, $P = .02$) and left posterior IC ($\eta^2_p = 0.10$, $P = .01$). Post hoc analyses revealed no significant differences across all ROIs between MCs and the TBI-passed subgroup. However, there were significant FA reductions in the TBI-failed subgroup for the right anterior IC (Cohen $d = 0.69$, $P = .04$), left cingulum (Cohen $d = 1.04$, $P = .01$), and left posterior IC (Cohen $d = 1.14$, $P < .01$) when compared with MCs.

TABLE 3 *Group comparisons of ROIs across DTI indices*

		Military Controls		TBI-passed		TBI-failed		P[a]		
	Track name	Mean	SD	Mean	SD	Mean	SD	Military Controls vs TBI-passed	Military Controls vs TBI-failed	TBI-passed vs TBI-failed
FA	AIC, left	0.413	0.017	0.410	0.020	0.408	0.030	0.55	0.49	0.78
	AIC, right	0.422	0.020	0.419	0.018	0.407	0.023	0.54	**0.04**	0.07
	CC body	0.493	0.020	0.498	0.016	0.487	0.014	0.24	0.33	**0.04**
	Cing, left	0.451	0.018	0.445	0.020	0.432	0.019	0.27	**0.01**	**0.04**
	Cing, right	0.430	0.018	0.428	0.019	0.417	0.021	0.71	0.06	0.08
	Fornix	0.381	0.032	0.386	0.019	0.381	0.017	0.40	0.91	0.58
	CC genu	0.475	0.030	0.475	0.026	0.461	0.023	0.99	0.14	0.11
	PIC, left	0.490	0.013	0.484	0.015	0.475	0.013	0.10	**0.00**	0.06
	PIC, right	0.485	0.018	0.479	0.017	0.475	0.015	0.18	0.09	0.39
	CC splenium	0.515	0.017	0.517	0.017	0.505	0.018	0.69	0.10	**0.03**
RD x10^{-4}	AIC, left	5.17	0.23	5.36	0.22	5.31	0.27	**0.00**	0.10	0.47
	AIC, right	5.13	0.24	5.26	0.19	5.29	0.20	0.02	**0.03**	0.73
	CC body	5.18	0.33	5.15	0.26	5.08	0.30	0.67	0.32	0.46
	Cing, left	4.97	0.23	5.08	0.19	5.14	0.19	**0.04**	**0.02**	0.36
	Cing, right	5.08	0.22	5.15	0.19	5.24	0.24	0.19	**0.03**	0.16
	Fornix	8.90	0.96	9.06	1.04	9.03	0.84	0.54	0.69	0.94
	CC genu	5.33	0.35	5.38	0.26	5.41	0.27	0.46	0.40	0.75
	PIC, left	4.58	0.20	4.66	0.16	4.69	0.18	0.09	0.08	0.59
	PIC, right	4.60	0.26	4.70	0.18	4.70	0.19	0.08	0.18	0.97
	CC splenium	5.29	0.33	5.30	0.28	5.28	0.31	0.92	0.88	0.80
AD x10^{-3}	AIC, left	1.00	0.05	1.04	0.05	1.02	0.05	**0.02**	0.30	0.40
	AIC, right	1.02	0.05	1.04	0.05	1.02	0.05	0.08	0.81	0.24
	CC body	1.19	0.06	1.21	0.06	1.16	0.05	0.29	0.13	**0.01**
	Cing, left	1.05	0.04	1.07	0.05	1.05	0.04	0.43	0.69	0.28
	Cing, right	1.03	0.04	1.04	0.05	1.03	0.04	0.43	0.71	0.81
	Fornix	1.63	0.14	1.67	0.17	1.66	0.13	0.22	0.52	0.77
	CC genu	1.18	0.06	1.20	0.06	1.17	0.04	0.31	0.43	0.10
	PIC, left	1.05	0.04	1.05	0.04	1.04	0.03	0.39	0.51	0.15
	PIC, right	1.04	0.04	1.06	0.04	1.04	0.04	0.20	0.96	0.32
	CC splenium	1.28	0.07	1.29	0.07	1.25	0.04	0.40	0.23	**0.05**

Abbreviations: AD, axial diffusivity; AIC, anterior internal capsule; Cing, cingulum bundle; CC, corpus callosum; FA, fractional anisotropy; PIC, posterior internal capsule; RD radial diffusivity; TBI, traumatic brain injury.

[a]Bolded P values indicate a value less than .05 ($P < .05$) and are significant.

Moreover, the TBI-failed subgroup demonstrated significantly lower FA for the left cingulum (Cohen $d = 0.67$, $P = .04$), and in the body (Cohen $d = 0.71$, $P = .04$), and splenium (Cohen $d = 0.69$, $P = .03$) of the CC in comparison with the TBI-passed subgroup. All other FA ROIs did not reach significance (all Ps $> .05$).

In regard to RD, there was a significant main effect of group for the left ($\eta^2_p = 0.09$, $P = .01$) and right ($\eta^2_p = 0.08$, $P = .03$) anterior IC, as well as for the left cingulum ($\eta^2_p = 0.09$, $P = .04$). Post hoc analyses revealed increased RD in the TBI-passed subgroup for the left (Cohen $d = 0.86$, $P < .01$) and right (Cohen $d = 0.63$, $P = .02$) anterior IC, in addition to the left cingulum (Cohen $d = .53$, $P = .04$) when compared with MCs. Similarly, increased RD in the TBI-failed subgroup was observed for the right anterior IC (Cohen $d = 0.71$, $P = .03$), in addition to the left (Cohen $d = 0.79$, $P = .02$) and right (Cohen $d = 0.71$, $P = .03$) cingulum relative to MCs. All other RD ROIs did not reach significance, nor were there any significant differences between the TBI-passed and TBI-failed subgroups detected (all Ps $> .05$).

Analysis of variance revealed a main effect of group for AD of the CC body ($\eta^2_p = 0.08$, $P = .04$). Post hoc analyses revealed that compared with MCs, the TBI-passed subgroup showed decreased AD for the left anterior IC (Cohen $d = 0.24$, $P = .02$), yet there were no significant differences between MCs and the TBI-failed subgroup across any ROI. However, the TBI-failed subgroup showed significantly reduced AD in the body (Cohen $d = 0.82$, $P = .01$) and splenium (Cohen $d = 0.68$, $P = .05$) of the CC, relative to the TBI-passed subgroup. All other AD ROIs did not reach significance (all Ps $> .05$).

Neuropsychological test performances

There were some violations of normality, yet all variances were homogeneous across the groups for each neuropsychological variable. Outliers were removed

TABLE 4 *Cognitive test performance by group*

Cognitive test	Military Controls Mean (SD)	TBI-passed Mean (SD)	TBI-failed Mean (SD)	*P*	*P*[a] Military Controls vs TBI-passed	*P*[a] Military Controls vs TBI-failed	*P*[a] TBI-passed vs TBI-failed
CVLT-II 1–5 total *T* Score	54.57 (10.06)	49.25 (9.79)	38.31 (7.80)	<.001	0.09	**0.00**	**0.01**
CVLT-II Long Delay Free Recall *Z* score	0.15 (1.10)	− 0.23 (1.10)	− 1.77 (1.09)	<.001	0.39	**0.00**	**0.00**
CVLT-II Total Recognition Discriminability	0.08 (1.05)	− 0.22 (1.01)	− 1.59 (1.13)	<.001	0.50	**0.00**	**0.00**
D-KEFS Letter Fluency Scaled Score	11.61 (2.86)	9.95 (3.33)	9.00 (2.58)	<.05	0.10	0.05	0.62
D-KEFS Category Fluency Scaled Score	12.35 (2.77)	11.17 (3.26)	9.00 (2.86)	<.05	0.31	**0.01**	0.09
D-KEFS Category-Switching Total Correct Scaled Score	12.65 (3.02)	10.65 (3.45)	8.25 (3.25)	<.001	0.06	**0.00**	0.07
D-KEFS Trails Number Sequencing Scaled Score	11.52 (2.19)	10.73 (2.49)	9.33 (2.71)	.05	0.43	**0.04**	0.20
D-KEFS Trails Letter Sequencing Scaled Score	11.39 (2.06)	10.51 (2.63)	9.42 (2.35)	.05	0.49	**0.04**	0.18
D-KEFS Trails Number-Letter Sequencing Scaled Score	10.91 (1.59)	9.37 (2.89)	7.17 (3.51)	<.005	0.07	**0.00**	**0.04**
WCST-64 Preservative Responses T-Score	47.41 (5.80)	46.95 (7.18)	48.08 (11.64)	.90	0.97	0.97	0.90
WCST-64 Total Errors T-Score	50.95 (5.73)	50.59 (7.19)	49.00 (13.69)	.79	0.98	0.79	0.83

Abbreviations: CVLT-II, California Verbal Learning Test-II Edition; D-KEFS, Delis-Kaplan Executive Function System; SD, standard deviation; TBI, traumatic brain injury; WCST-64, Wisconsin Card Sorting Test- 64 Card Version.
[a]Bolded *P* values indicate a value less than .05 ($P < .05$) and are significant.

prior to group analyses and the Kruskal-Wallis tests revealed the results did not differ from ANOVA results. Analysis of variance results are presented in Table 4. One-way ANOVAs revealed significant group differences across CVLT-II and D-KEFS variables (all $P < .05$), and post hoc comparisons revealed that the TBI-failed subgroup performed significantly worse than both MCs and the TBI-passed subgroup across multiple tests (all Ps $< .05$). When the TBI-Passed subgroup was compared with MCs, no significant results were revealed but the TBI-Passed subgroup generally demonstrated more poor performance.

CONCLUSIONS

Using DTI, we explored neuroimaging biomarkers of WM microstructure in Veterans with history of mTBI who failed PVTs, those with mTBI who passed PVTs, and MCs with no neurotrauma history. The groups significantly differed in FA-WMB, an aggregate score reflecting the number of ROIs in which there is a significant deviation from the control mean. Specifically, the TBI-failed subgroup showed greater WMB when compared with either MCs or TBI-passed subgroups; and no significant differences in WMB were observed between MCs and the TBI-passed subgroup. Exploratory analyses of WM tracts revealed decreased WM integrity across *both* TBI subgroups when compared with MCs. Furthermore, in line with our WMB findings, there were significant WM alterations across several ROIs in the TBI-failed subgroup relative to the TBI-passed subgroup. Finally, significantly lower cognitive scores were observed in the TBI-failed group relative to both the MCs and TBI-passed group.

Although some studies show notable and robust abnormalities of WM microstructure in both civilians and Veterans with mTBI when compared with control groups,[71–74] other studies have failed to find such differences.[75–77] Reasons for variability across studies remain unclear but could be related to heterogeneity of diagnostic criteria used,[78,79] differences in clinicpathologic characteristics of mTBI,[80] and variation in imaging acquisition or analysis techniques.[81,82] Further complicating matters, many MCs are exposed to blast during their service, and there is debate regarding whether blast exposure causes measurable brain structural alterations.[83,84] General exposure to blast may obscure group differences between controls and mTBI participants.

Contrary to expectations, comparisons between the TBI subgroups revealed a *greater* degree of overall WM damage in the TBI-failed subgroup when compared with the TBI-passed subgroup. Examination of WM ROIs showed a similar pattern and revealed an increased level of WM microstructural abnormalities across commissural tracks in the TBI-failed subgroup relative to the TBI-passed subgroup. Those with poor PVT performance in our study generally displayed worse WM integrity and reported elevated psychiatric symptoms. Thus, those who fail PVTs may subjectively experience greater cognitive or psychiatric difficulties than those who pass PVT measures *because* of greater underlying brain abnormalities. Consistent with this possibility, a study by Lippa and colleagues[85] showed that poor PVT performance, above and beyond various demographic and injury factors, predicted less community integration and participation in Veterans with mTBI. Findings of their study are of particular importance as the veracity of impairment may be called into question due to poor PVT performance. Results of this study align with those of Lippa and colleagues[85] and underscore the possibility that individuals who fail PVTs may in fact experience considerable difficulties and be in need of clinical resources, as the increased symptom endorsement, albeit potentially exaggerated, may be associated with genuine structural impairments.

Although we failed to detect differences between MCs and the TBI-passed group on our global measure of WM integrity (WMB), ROI analyses revealed WM alterations across both TBI subgroups relative to MCs. More specifically, both TBI subgroups demonstrated consistent WM alterations in the anterior IC and cingulum. Importantly, these fronto-limbic and fronto-striatal tracts connect regions critical for emotional and higher-order cognitive functioning and may be especially vulnerable to shear and tensile strain that occurs during neurotrauma.[86,87] In addition, ROI analyses between the TBI-passed and TBI-failed subgroups revealed significantly decreased FA and AD in the body and splenium of the CC in the TBI-failed subgroup. As detailed in a meta-analysis by Aoki et al,[88] the unique organization of the CC may contribute to its increased vulnerability to neurotrauma when compared with less organized tracts. Furthermore, the falx cerebri may come into contact with the anterior and posterior aspects of the CC, acting as a fulcrum in the mechanical distortion of the CC during trauma. As such, disrupted interhemispheric communication, or integration of the CC with frontal and temporal lobes, may play a pivotal role in the clinical presentation of the TBI-failed subgroup. Mechanisms behind lower FA-WMB in the TBI-failed subgroup are unclear. The TBI-failed subgroups reported slightly greater LOC durations and were closer in proximity to incurred head injuries; thus, it is possible that the increased WM damage within the TBI-failed subgroup may be the product of more severe[75] and less remote injuries.[89] It must be acknowledged that a number of studies have demonstrated associations between DTI-measured WM differences and psychiatric symptoms.[90–92] In other words, it is possible

that WM damage contributes to increased psychiatric symptomatology within the TBI-failed subgroup and better explains observed WM differences between the groups.

Clinical decision making in the context of PVT failure is complex, and several theories have been proffered to explain possible factors behind poor PVT performance. Bigler[26,27] has noted that at least some PVT failures may be related to neurological deficits,[25,93,94] or disruption of brain regions actively engaged during PVT performance (see Bigler[26] for review). For example, performance during the Word Memory Test, a commonly used PVT, initiates activation of fronto-executive neural systems,[95,96] which have been linked to structural impairments in both civilians and Veterans with mTBI.[73,74] In addition, the practice of dichotomizing PVT performance may be limiting, as useful information may be gleaned from the evaluation of PVT performance on a continuum.[26,27,97] Clearly, additional research examining these proposed hypotheses–especially in the context of neuroimaging findings–is needed.

To the best of our knowledge, this represents the first study to compare the structural integrity of cerebral WM tracts between those who pass and fail PVTs in the context of military TBI. However, there are some weaknesses of our study that are important to note. For example, diagnosis of TBI within this study relies largely on retrospective self-report and may be subject to recall bias, although this is a common limitation in TBI assessment, and it must be acknowledged that these time differences may have caused differential effects between the groups.[98] Importantly, the reliability and validity of the TBI measure utilized has not been established, although such efforts are currently underway. In addition, poor PVT was defined by reduced performance on at least 1 of 2 measures, and the application of stricter criteria[99] may have yielded different findings. The majority of those with poor PVT performance in our study failed the CVLT-FCR ($n = 9$), as opposed to the TOMM ($n = 3$), which may be a reflection of varying degrees of sensitivity and specificity of each test. Moreover, recently, there has been a distinction made between PVTs and symptom validity tests,[100] as symptom validity tests may better speak to self-reported symptomatic complaints. Furthermore, although our sample is likely representative of OEF/OIF/OND Veterans with history of mTBI, our current sample was relatively small, and therefore sampling bias must be considered and replication of these findings is needed. Finally, due to the exploratory nature, ROI analyses were not corrected for multiple comparisons; thus, there is an increased likelihood of type I error.

Taken together, our results demonstrate that WM microstructural alterations were evident in a sample of Veterans with mTBI who failed PVTs, and the extent of WM damage in this subgroup was unexpectedly greater than those with mTBI who passed PVTs. Results of this study highlight that, despite the understandable cautious interpretation of cognitive scores in the context of poor PVT performance, such individuals may still have genuine deficits owing to the presence of WM abnormalities. As our understanding of the relationship between measures of WM microstructure and cognitive functions improves, DTI may represent an invaluable marker and objective measure of WM damage and poor clinical outcome.

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Pathological Vascular and Inflammatory Biomarkers of Acute and Chronic Phase Traumatic Brain Injury

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Abstract

Given the demand for developing objective methods for characterizing traumatic brain injury (TBI), research dedicated to evaluating putative biomarkers has burgeoned over the past decade. Since it is critical to elucidate the underlying pathological processes that underlie the higher diverse outcomes that follow neurotrauma, considerable efforts have been aimed at identifying biomarkers of both the acute and chronic phase TBI, Such information is not only critical for helping to elucidate the pathological changes that lead to poor long-term outcomes following TBI, but it may also assist in the identification of possible prevention and interventions for individuals who sustain head trauma. In the current review, we discuss the potential role of vascular dysfunction and chronic inflammation in both acute and chronic phase TBI, and we also highlight existing studies that have investigated inflammation biomarkers associated with poorer injury outcome.

Pathological Vascular and Inflammatory Biomarkers of Acute and Chronic Phase Traumatic Brain Injury

Traumatic brain injury (TBI) is frequently associated with persistent behavioral, cognitive, and psychosocial changes, many of which have important implications for daily functioning. Growing evidence furthermore suggests TBI should be conceptualized as a dynamic process that can affect brain health, directly and indirectly, several years after the initial insult [1-6]. Indeed, there have been repeated reports of persistent neurologic symptoms and an increased risk for the long-term development of neurodegenerative conditions, such as Alzheimer's disease (AD) and chronic traumatic encephalopathy (CTE) [7-12] in individuals who have sustained even mild forms of neurotrauma. Accordingly, there have been rapid developments in the clinical tools and measures used to identify and characterize neurotrauma both in terms of acute and long-term neuropathological effects of the injury. The use of biological markers, or biomarkers, for TBI diagnosis and prognosis may help clinicians more accurately identify when TBI has occurred, in addition to providing useful information about the underlying neuropathological mechanisms involved with poor injury outcome in the long-term. This review will thus discuss the evidence for the utility of fluid biomarkers in the identification of TBI. Specifically, in the context of both acute and chronic TBI, we will underscore the role of vascular dysfunction and chronic inflammation in secondary injury following TBI; (2) highlight studies emphasizing inflammation biomarkers; and (3) discuss genetic factors associated with poorer injury outcome. When possible, the applicability of the available biomarker literature to mild forms of TBI is examined, with

a particular emphasis on the need for future explorations of acute and chronic phase biomarkers across the entire TBI severity spectrum.

Characteristics of TBI and Tissue Injury Mechanisms

There are several different ways in which TBI can be classified, including (1) the source of force causing the injury; (2) injury severity; and (3) mechanism of brain tissue damage. Penetrating TBI occurs when an impacting object penetrates all the protective layers surrounding the brain (i.e., skin, skull, and meninges), directly inflicting injury to the brain tissue. This type of TBI is often complicated by hemorrhage, edema, and inflammation, and is associated with a variety of poor outcomes (e.g., post-traumatic seizures, infection, cognitive and functional impairment, death). Given the severity and complexity of penetrating TBI, our current understanding of the pathophysiology and clinical outcome of penetrating TBI in humans has been largely limited to clinical case studies, observational studies utilizing small research samples, and post-mortem neuropathological studies. Recent advances in TBI animal research have demonstrated some promising rodent models of penetrating TBI that may further elucidate the pathophysiological mechanisms that underlie clinical outcome [13]. Comparatively, non-penetrating or closed head trauma can be sustained through the application of both blunt and blast forces to the head. While the physics involved in the injuries sustained from these forces are distinct, the degree to which the resulting pathological processes and long-term clinical sequalae may differ remains unclear. In recent years, there has been an expansion expansion in both human and animal studies attempting to model the neuropathology and clinical outcome of non-penetrating TBI.

Per the American Congress of Rehabilitation Medicine (ACRM), the severity of TBI is ranked on a scale from mild to severe based on the presence and degree of an alteration of mental state (AMS), posttraumatic amnesia (PTA), and loss of consciousness (LOC). These criteria categorize head trauma using the following severity scale: (1) no TBI is defined as a head injury that does not result in AMS, PTA, or LOC; (2) mild TBI is defined a traumatically induced physiological disruption of brain dysfunction, as indicated by any AMS, LOC of 30 minutes or less, PTA no greater than 24 hours, or Glasgow Coma Scale (GCS) of 13-15; (2) moderate TBI is defined as a head injury that results in an LOC of 30 minutes to 24 hours, or AMS and/or PTA of greater than 24 hours; and (4) severe TBI is a head injury that result in LOC greater than 24 hours and/or PTA that lasts for more than seven days [14]. Lastly, both primary and secondary mechanisms have been identified through which neural tissue injury is sustained following TBI. In contrast to primary injury, which describes the result of mechanical forces applied to the skull and brain at the time of impact, secondary injury, though poorly understood, is believed to represent damage to brain tissue that evolves over time [15-16]. Importantly, it is this mechanism of damage that is thought to underlie the long-term effects mTBI.

Vascular Dysfunction and TBI Secondary Injury.

Injury mechanisms in TBI.

There are important biophysical differences between blunt and blast force neurotrauma. Understanding these differences may serve a critical role in understanding neuropathological and clinical sequalae of TBI, especially along the mild end of the

severity spectrum [17]. For example, blunt impact to the head may cause scalp tissue damage, fracture or depression of the skull, coup/countercoup impact of the brain tissue against the inner walls of the cranial vault, and altered intracranial pressure gradients [18]. Accordingly, fractures or depressions of the skull can displace underlying neural tissue (i.e., mass effect, creating localized displacement of neural tissue within the skull cavity). Similarly, coup/countercoup impact can result in focal contusions of cortical tissue, most commonly occurring in places in which the brain is most constrained or adjacent to ridged bony structures in the cranial cavity (e.g., anterior fossa, orbital sockets) [19]. Rapid acceleration/deceleration forces on the brain that are either linear or rotational in nature can also occur following blunt force neurotrauma [20]. Theses forces stretch and deform brain tissue, exerting stress on neurons, glial cells, and blood vessels, as well as altering membrane permeability. This ultimately results in damage to neuronal cell bodies, axons, dendrites, blood vessels, and glial cells [21-22]. Focal and/or diffuse axonal injury (DAI)—characterized by enlarged axons with microtubule damage—is thus commonly observed following blunt force mTBI. Interestingly, DAI tends to occur in brain regions with adjacent tissues of notably different densities (e.g., grey-white matter junctions). Such regions likely incur increased shearing stress due to the different rates at which the adjacent tissues move in response to the blunt force impact.

The biomechanics of blast force neurotrauma, while sharing some aspects in common with blunt force trauma (e.g., force applied to head, which is loaded onto skull and brain tissue differentially), includes some characteristics that make it both distinct and complex relative to other forms of neurotrauma. While many of these characteristics are related to the physics of the shockwave itself (e.g., blast overpressure and

underpressure), an additional layer of complexity is involved with the environment in which blast force mTBI occurs (e.g., thermal heating, acoustic waves, radiation). While several disputed mechanisms have been put forth due to the additional complexity of characterizing the biophysics of blast induced mTBI, many of these mechanisms center around the notion that exposure to a blast shockwave overpressure results in a distortion neural tissue and bodily fluids that has deleterious effects on the brain at both microbiological and gross morphological levels [23-24]. For example, it has been proposed that the quick changes in air pressure (shock wave) following an explosion leads to rapid acceleration and deceleration of neural tissues, exerting sheering forces that ultimately result in diffuse axonal injury in blast-induced mTBI [25-26]. Another proposed mechanism relates to disruption of blood brain barrier (BBB)—a highly selective vascular structure that controls the movement of molecules between peripherally circulating blood and central nervous system (CNS)—due to the primary impact of the shockwave to the abdomen whereby kinetic energy from the shock wave is transferred into hydraulic pressure when it meets bodily fluids. This results in the rapid physical displacement of blood from the abdominal cavity to the cranial cavity, damaging small brain vessels and disrupting the BBB [15, 27-30].

Common pathological sequalae in TBI.

Irrespective of mechanism, both blast and blunt-force neurotrauma generally appear to result in acute neural, glial, and vascular damage with similar pathological sequalae. While damage to parenchymal tissue has historically been the focus of TBI research, an increasing number of studies have highlighted the central role of cerebrovascular and alterations and dysfunction in both *acute and chronic* effects of

neurotrauma; for in-depth reviews, see [3-5]. Importantly, mounting evidence suggest that the acute vascular damage (e.g., torn or broken vasculature, microbleeds, endothelial cell damage, BBB damage, altered cerebral blood flood [CBF]) and neuroinflammation (e.g., activation of microglia, gliosis and aggregates of activated macrophages) that occur from the immediate blunt or blast impact may trigger and perpetuate a host of *secondary* pathophysiological cascades (i.e., chronic neuroinflammation; edema; changes to the autoregulation of CBF, neurovascular uncoupling, and ischemia/hypoperfusion; hemosiderin deposits), ultimately promoting brain degeneration and dysfunction. Additionally, increased extravasation of peripheral immune cells, which are not normally found in the CNS due to their neurotoxicity in aggregate, may ultimately be promoted by decreased BBB in both acute and chronic phase neurotrauma [31]. Thus, while the complex molecular and cellular mechanisms responsible for the heterogeneous array of outcome following TBI are not fully understood, the presence of these chronic, insidious pathological processes may indeed be responsible for the poor long-term outcomes reported in some individuals following TBI.

Biomarkers of Acute and Chronic Pathological Processes Following TBI.

Markers of Inflammation.

It is well documented that there are alterations of various neuroinflammatory process following TBI [32]. In addition to increased immuno-regulatory activity in CNS cells, peripheral immune cells and molecules have also been observed to cross the BBB in response to TBI [33-34]. Various pro- and anti-inflammatory agents, such as tumor necrosis factor (TNF), IL-1β, IL-6, IL-8, and IL-10 in particular, have been observed to

fluctuate in response to TBI [35-36], and have thus been investigated as putative biomarkers for TBI diagnosis and prognosis.

TNF. Broadly, the tumor necrosis factor superfamily refers to a group of cytokines involved with initiating and promoting cellular death. Within this superfamily, the TNF cytokine (previously referred to as TNF-α) represents a well-studied and highly versatile cytokine. While TNF is frequently studied in relation to its potent pro-inflammatory characteristics [37], it has also been observed to serve anti-inflammatory functions [38]. TNF is specifically expressed early in the response to neuronal injury, and has a major role in initiating neutrophil and monocyte recruitment to the site of neuronal damage [39-40].

In previous studies employing animal models of TBI, increases in parenchymal levels of TNF have been detected as early as one hour following TBI, and appear to peak four to eight hours following the initial injury [41-45]. The time course of TNF alteration in cerebrospinal fluid (CSF) differs from that in brain tissue, peaking at approximately 24 hours following TBI [46]. Research employing animal models of mTBI specifically have suggested that TNF levels may not be sensitive to mild neurotrauma [e.g., 44]; however, here is some recent evidence to suggest that alterations in TNF levels can be detected in mTBI. One study found significant increases in TNF in rodents experiencing mild lateral fluid percussion (LFP) injury as early as 3 hours after the injury [47]. In another study, researchers observed significant increases in TNF in the hippocampus region of rodents induced with mild blast brain injury at 6-hours post-injury [48]. A more recent study also reported that increases in serum levels of TNF were observed four hours post-injury in a closed skull weight-drop model of mTBI [49].

In humans, elevated TNF concentrations in serum, plasma, and CSF following TBI across the severity spectrum have also been reported [50-52], and appear to be increased in head injured samples when compared to control groups [53-54]. Similar to animal models of TBI, CSF protein levels of TNF appear to peak within 24 hours in severe TBI [55], although some studies have reported multiple post-injury peaks of TNF levels when recorded over the course of several weeks post injury [54]. Additionally, TNF mRNA and protein, are among pro-inflammatory cytokines (i.e., IL-8, IL-1β) that have been observed to increase within minutes of TBI in post-mortem brain tissue, indicating that a cerebral inflammatory cascade is initiated acutely following severe neurotrauma [56]. However, while this evidence suggests that TNF is involved in the neuroinflammatory response to severe TBI, research investigating TNF as a predictor of TBI outcome has produced mixed findings. Several small studies of severe TBI have reported no association between serum TNF levels and increased intracranial pressure (ICP), prognosis, or mortality [55, 57]. These studies are corroborated by a larger study reporting similar findings, with no relationship observed between initial TNF levels in both CSF and serum with GCS, ICP, or neurological outcome in acute phase severe TBI [58]. Conversely, more recent studies have reported an association between serum concentrations of TNF with increases in ICP, decreases in cerebral perfusion pressure (CPP), and poorer six-month outcome (extended Glasgow outcome scale [GOSE]) in patients who sustained moderate or severe TBI [59-60]. A similar relationship was not observed for CSF TNF levels, suggesting that serum TNF levels may be more sensitive predictors of severe TBI outcome than CSF protein levels [60]. In sum, there is evidence that TNF is elevated in the acute phase on injury. This is largely derived from research

employing animal or human models of moderate to severe TBI, although there is some data to suggest that acute elevations in TNF occur in mTBI as well. Additionally, research aimed at characterizing the relationship between acute phase increases in TNF and outcome are mixed, and there appears to be no existing investigations on chronic phase TNF elevations and associated outcome in humans.

IL-1β: Interleukin-1β is a highly regulated, potent pro-inflammatory cytokine that is released by macrophages and monocytes [61-62]. Although its primary role is regulation and release of other cytokines, IL-1β is also involved in a variety of cellular activities, including cell proliferation, differentiation, and apoptosis. It has also a reported role in certain brain pathologies that are common following TBI (e.g., BBB damage [63], cerebral edema [64], and has been implicated as having a role in certain chronic diseases that are prevalent in the aging population (e.g., cancer [65], neurodegenerative disease [66-67]).

Previous research using both animal and human models of TBI have reported an acute global increased in IL-1β mRNA, protein, and activated caspase-1 (activated form of the IL-1β converting enzyme) in *post-mortem* brain tissue following TBI [56, 68]. However, much more inconsistent findings have been reported regarding IL-1β levels in serum and CSF, with several studies reporting weak or no associations in severe TBI [69-72] and others reporting a significant increase following severe TBI [e.g., 73]. Despite this discrepancy in the literature, several studies have demonstrated the predictive value of serum and CSF levels of IL-1β as it relates to TBI outcome. High CSF and serum concentrations of IL-1β have been associated with poorer three- and six-month outcome (i.e., GOS; recovery vs. moderate-severe disability) as well as increased ICP following

severe head trauma in both pediatric and adult populations [55, 58, 72, 74-75]. Furthermore, in a more recent prospective cohort study, IL-1β was not only reported to be elevated over 3 months following TBI, but was significantly associated with increased odds of unfavorable outcomes at 6 months following severe head injury (GOS) [76]. Because of such reported associations between acute and chronic IL-1β levels and outcome, some intervention trials using animal models of TBI have also explored IL-1β expression as a potential target for treatment of TBI. For example, Lee et al. [77] reported that pharmacologically induced hypothermia was associated with decreases in mRNA expression of IL-1β and TNF were associated with improved sensorimotor functional recovery in mice after TBI. The goal behind such research has been to determine whether decreasing the levels or inhibiting the effects of pro-inflammatory processes positively affects TBI outcome. Findings from this line of research not only provide useful information regarding potential treatments for TBI, but also support the notion that chronic inflammation may be the mechanism through which secondary neural injury following TBI may be sustained. But while this line of research appears promising for TBI interventions along the severe end of the injury spectrum, it remains unclear whether acute and chronic alterations in IL-1β expression occur following mTBI, and more over whether limiting the expression of this inflammatory marker can serve as a potential target for treatment of TBI.

IL-6. Interleukin-6 (IL-6) is one of the most well studied inflammatory markers across a variety of populations. In the CNS, IL-6 is expressed by astrocytes, microglia, and neurons [78-82]. In humans, IL-6 does not typically exist at detectable levels in serum under normal physiological conditions [83-84]; however, increases in IL-6 have

been observed under pathophysiological conditions, and are believed to be indicative of axonal damage [85-86]. There is also evidence for involvement of IL-6 in several normative and pathological physiological processes, including aging, TBI, inflammation, immunity, and neural development [87-88]. Notably, IL-6 has also been associated with AD for which TBI and aging is considered to be a prominent risk factor [89-90]. Given these various associations between IL-6 and disease conditions, IL-6 is a particularly interesting target for studying the chronic effects of mild TBI.

IL-6 appears to be a highly sensitive biomarker for neurotrauma. While undetectable in the normal brain, rodent models of TBI reveal an acute increase in IL-6 expression following TBI [82, 91]. In human, IL-6 concentrations have been reported to acutely, and sometimes persistently, increase following severe TBI [35, 51, 71, 76, 92]. This up-regulation of the pro-inflammatory cytokine is easily detectable following acute TBI, although reports reflect some degree of variability in this response. CSF concentrations have been reported a significant increase following TBI, reaching a maximum peak within 3 to 6 days post injury [69, 93]. Comparatively lower, but still detectable, alterations in IL-6 concentrations have been observed in both blood serum and plasma [35, 74, 94]. TBI severity has also been related to the intracranial IL-6 gradient in the blood of trauma patients at the time of hospital admission, with higher gradients associated with greater injury in severe TBI [95].

Given the pro-inflammatory role of IL-6 in the brain, the prognostic value of IL-6 levels following TBI has been investigated in several studies. In one study, elevated IL-6 serum levels within the first 17 hours following severe brain injury effectively identified patients at risk of developing problematic levels of intracranial pressure (ICP) [71].

Similarly, higher blood IL-6 intracranial gradients at the time of hospital admission were observed in brain trauma patients with fatal outcome in the six months following, compared to survivors [95]. More recently, Ferreira et al. [96] reported significant increases in IL-6 in non-survivors with severe TBI compared to survivors. In direct contrast, a study that used intracranial microdialysis to measure IL-6 concentrations in brain parenchyma reported that higher IL-6 levels were observed in survivors of severe TBI compared to non-survivors [94], a finding that suggests that IL-6 serves a neuroprotective function rather than a risk factor for TBI poor outcome. These findings, however, conflict with other reports of IL-6 as a significant predictor of poor outcome following pediatric TBI (GCS and GOS) [97-98].

Although there is a clear relationship between increased IL-6 expression in the brain and TBI, there are several characteristics of the cytokine that render it a poor predictive biomarker for TBI (when it is used in isolation). IL-6 is not exclusively expressed in the brain, or in response to head trauma. Accordingly, IL-6 concentrations are sensitive to the presence of peripheral injuries, such as burns [99] and orthopedic injuries [71]. Additionally, IL-6 had no prognostic value in predicting elevated ICP following severe TBI in patients with polytrauma, which was in stark contrast to its high sensitivity in individuals with TBI only [71]. An additional challenge with IL-6 is that its serum levels may be more indicative of BBB integrity than brain concentrations of the cytokine. This is suggested by the limited ability of IL-6 to cross the BBB [100], involvement of a transport mechanism to cross the BBB [101]. Thus, the presence of IL-6 following a possible TBI should be interpreted with caution. Taken together, both animal and human research in severe TBI suggests that IL-6 may be a sensitive (but not specific)

biomarker for acute phase TBI and associated outcome, with more limited evidence for the role of IL-6 in the putative protracted neuroinflammatory response thought to characterize chronic phase TBI. Despite these findings, minimal human research has been conducted to explore the utility of the IL-6 biomarker in mTBI.

IL-8. Interleukin-8 (IL-8), or CXCL8, is a member of a special class of small cytokines called chemokines. It is secreted by a variety of cells, including glial cells, macrophages, and endothelial cells [102-104]. IL-8 is released from astrocytes in the presence of other cytokines that are acutely expressed following a TBI, such as TNF or IL-1β [105]. Once expressed, IL-8 induces chemotaxis and phagocytosis of neutrophils, attracting them to the site of neural damage and clean up debris resulting from the injury [106]. While neutrophils typically leave the brain by one week following a brain injury, macrophages have been reported to linger for roughly four weeks [107]. This prolonged presence of activated leukocytes in the brain is neurotoxic, and has been suggested to contributed to the ongoing neuronal damage that occurs following the acute brain injury. In addition to being studied as a potential biomarker for TBI, increased IL-8 expression has also previously been linked to cardiovascular disease [108], and is known to be a potent promoter of angiogenesis [109]. This relationship between IL-8 and cardiovascular functioning has important implications for both TBI and aging, and furthermore may be reflective of a shared or synergistic relationship between the underlying pathological mechanisms involved with cerebrovascular disease, pathological aging, and chronic TBI.

Along with several other pro-inflammatory cytokines, several studies have reported both acute and persistent increases in IL-8 levels following severe TBI [53, 70, 76, 110-111]. The greatest increases in IL-8 concentrations are observed in CSF [110-

111], but have also been observed to a lesser degree in serum after severe injuries [70, 76, 110, 112]. While the increase in IL-8 is much greater in CSF compared to serum, several studies have demonstrated the prognostic value of blood-based IL-8 levels following head injury. For example, significantly lower acute plasma, and not CSF, levels of IL-8 has been observed in survivors of severe TBI, compared to non-survivors [96, 113]. Similarly, serum IL-8 levels at 12 [112] and up to 3 months [76] following TBI have been observed to be predictive of long-term functional outcome (i.e., GOS). These observational studies of TBI outcome have been further corroborated by human autopsy studies investigating the relationship between post-mortem expression chemokines and antemortem TBI. For example, the up-regulation of IL-8 mRNA and proteins was observed in post-mortem in injured brains compared to controls [56]. Importantly, the overexpression of IL-8, as well as other chemokines, was associated with the presence of CD68-positive macrophages and GFAP-positive reactive astrocytes. In sum, the available studies on IL-8 alterations following severe TBI suggest that there exists both acute and chronic increases in the expression of this pro-inflammatory marker. Furthermore, it appears that increases IL-8 levels within both injury phases is associated with poorer injury outcome; however, like the available literature on other pro-inflammatory cytokines, there is a lack of studies aimed at characterizing the role of IL-8 in acute and chronic mTBI. Thus, while there is evidence to suggest that IL-8 may serve as a potential biomarker for acute and chronic phase severe TBI, additional animal and human research is needed to determine its utility as a biomarker for mTBI.

IL-10. Contrary to the inflammatory makers previously covered in this review, interleukin-10 (IL-10) appears to act primarily as an anti-inflammatory cytokine.

Importantly, IL-10 has an inhibitory effect on the production of several pro-inflammatory mediators, ultimately serving to regulate many of the cytokines that have been linked to acute and chronic inflammatory processes. Particularly relevant to inflammation following severe TBI is its effect of IL-10 on IL-1β and TNF, and interferon (IFN), all of which have been observed to exert detrimental effects on the brain [114-115]. Indeed, previous studies on the effects of IL-10 in normal physiological conditions, as well as in the treatment of certain pathological conditions, have implicated IL-10 as having a potential role in reducing the negative effects of neuroinflammation in TBI [116-121]. Additionally, IL-10 expression appears to increase within the first 24 hours following a severe head trauma [35, 49, 54, 122], and, consistent with anti-inflammatory properties, this increase in IL-10 has been reported to correspond with a decrease in TNF levels. However, despite this well-documented anti-inflammatory role of IL-10, increased IL-10 following TBI has been repeatedly linked to poor outcome and mortality in both pediatric and adult severe TBI [58-59, 96, 123-125]. Additionally, higher IL-10 levels measured at 10 or 30 hours following severe TBI have also been found to be 6 and 5 times, respectively, more likely to result in hospital mortality compared to lower levels [125]. A possible explanation for this relationship is that the *relative* increases in pro- compared to anti-inflammatory cytokines, rather than the individual increase in IL-10, is important in predicting TBI outcome. Recent findings from a prospective cohort study support this notion, where the *ratio* of pro-inflammatory burden relative to IL-10 was found to be associated with unfavorable outcome following severe TBI [76]. That is, higher levels of pro-inflammatory IL-6, relative to anti-inflammatory IL-10, was significantly associated poorer GOS scores six months following severe TBI.

Research using animal models of head injury has also demonstrated the potential protective role of IL-10. For example, treatment of rats subjected to lateral fluid percussion-induced TBI with IL-10 has been shown to improve neurological recovery and reduced levels of IL-1β and tumor necrosis factor a (TNF) in brain tissues [126]. Similarly, local administration of IL-10 at the injury site attenuated the number and the hypertrophic state of reactive astrocytes and microglia and diminished TNF mRNA expression [127]. In a more recent study using a murine model of TBI, pharmacologically induced hypothermia (PIH) following controlled cortical impact decreased mRNA expression of pro-inflammatory cytokines (TNF-α and IL-1β), but increased IL-6 and IL-10 levels [77]. Sensorimotor function was also improved in PIH, providing further evidence for the altering the ratio of pro- and anti- inflammatory cytokines, such as IL-10, as a potential target for improving TBI outcome. It should be noted that certain studies have reported, however, an association between IL-10 increases and mortality. Specifically, Ferriera et al. [96] reported significant increases in IL-10 levels in in non-survivors with severe TBI relative to survivors of the injury. Although there appears to be converging evidence that IL-10 alterations occur during acute and chronic phase severe TBI, the predictive role of the biomarker for injury outcome remains unclear. Additionally, there is limited research on IL-10 following mTBI within both the acute and chronic phases of injury.

Genetic Factors.

Although not always discussed in relation to biomarkers for TBI, the role of genetics in the identification of effective biomarkers for TBI diagnosis and prognosis is one of critical consideration. That is, given that the environment in which acute and

chronic pathological mechanisms following TBI occur is strongly influenced by genetic factors, it is necessary to understand how certain genes may influence the presentation or overall nature these mechanisms. Although there are a multitude of genetic factors that affect brain structure and function, APOE and BDNF are the two most prominent in the TBI literature.

APOE. Apolipoprotein (APOE) is one of the most widely studied genes in the context of neurotrauma and recovery [128]. APOE is a protein largely associated with lipid and cholesterol transport as well as plasma lipoprotein metabolism in the central nervous system (CNS), all of which are essential for synaptogenesis [129]. Three APOE polymorphisms encode one of the three isoforms: APOE-ε2, APOE-ε3, and APOE-ε4. A loss in normal APOE function has been observed in APOE-ε4 carriers, negatively impacting synaptic plasticity and neuronal recovery from neurodegeneration [130-131]. The presence of the ε4 allele has been characterized as a major risk factor for the development of Alzheimer's disease [132-133]. This allele has also been linked to more abundant levels of amyloid beta (Aβ) plaque accumulation, which has been largely associated with AD [128]. APOE-ε4 promotes neuronal cell death, resulting in accelerated neurodegeneration [134]. APOE-ε4 has also been considered a major risk factor for various inflammatory metabolic diseases [134]. Relative to APOE-ε2 or APOE-ε3, APOE-ε4 has been associated with greater pro-inflammatory activity [129, 135], increased numbers of APP-immunoreactive axonal varicosities, and greater total human tau accumulation independent of injury status [136]. This indicates a potential primary effect of APOE-ε4 on the severity of axonal injury in acute TBI.

As previously discussed, disruption of the BBB caused by TBI allows immune cells to cross into the brain, stimulating a cascade of inflammatory responses 15, 27-30, 137]. This subsequently results in a series of molecular events, including apoptosis, inflammation, microglial activation, altered plasticity, and neuronal regeneration [21-22, 138-139]. Microglial activation prompts perivascular macrophage production of cytokines integral in modulating secondary injury as well as recovery after injury [138]. Compared to APOE-ε3 macrophages, APOE-ε4 macrophages have demonstrated impaired efferocytosis, the process by which apoptotic or necrotic cells are removed through the process of phagocytosis, in mouse models [134]. APOE-ε4 has also been found to potentiate endoplasmic reticulum stress and is associated with increased susceptibility to apoptosis in mice [134]. These findings indicate that APOE-ε4 has a role in promoting macrophage dysfunction. This further suggests a possible mechanistic link between APOE-ε4 and TBI secondary injury, as immune suppression following TBI has been found to slow brain infrastructure healing [140]. APOE-ε4 expression is also associated with a reduction in cerebral vascularization, thinner vascular walls, and decreased glucose uptake, compared to APOE-ε2 and APOE-ε3 expression [141]. This suggests an association between APOE-ε4 expression and BBB disruption, providing a possible link between APOE-ε4-induced BBB anomalies and TBI secondary injury.

BDNF. Brain derived neurotrophic factor (BDNF) is a polypeptide growth factor found in both the CNS and periphery. BDNF has been observed to serve a critical role in both neuronal survival and death within the central nervous system [142-143], as well as modulation of synaptogenesis and neurodevelopment throughout the human lifespan [144-147]. BDNF has been implicated in both normative neurocognitive functioning, as

well as the pathophysiology in certain psychiatric conditions (e.g., bipolar disorder, post-traumatic stress disorder) [148-151]; however, recent research has suggested that polymorphisms in the BDNF gene may have a large influence on determining the role of BDNF in such conditions [152-153].

The most well studied BDNF polymorphism involves the substitution of a single amino acid, Valine, with Methionine at codon 66 (Val66Met). The prevalence of this BDNF polymorphism, including both heterozygous ("Val/Met") and homozygous ("Met/Met") forms, has been estimated to be approximately 30-50% in the world population [154]. Importantly, the presence of the Met allele has been related to abnormal BDNF trafficking and activity-dependent secretion in neuronal cells [155-156]. Given the role of secreted BDNF in synaptic plasticity and neuronal survival in adulthood, the potential influence of BDNF genotype on mTBI outcome has been considered. With respect to TBI, the presence of the Met allele has been associated with better outcome following head injury, including improved cognitive recovery [157-159], preserved general intelligence [160], and survival probability [161]. The presence of the Met allele has further been associated with better overall cognitive functioning following severe TBI [157, 161]; however, evidence for whether this effect varies across cognitive domains is currently mixed [158, 162]. The relationship between BDNF polymorphisms and TBI cognitive outcome are particularly interesting, given that it differs from observed effects in healthy individuals and other psychiatric conditions [157, 160-161]. That is, the BDNF polymorphism appears to be protective under the pathophysiological conditions of TBI, but detrimental under other circumstances.

In sum, the association between BDNF polymorphisms and cognition post-injury appears to be complex. There is some evidence that the relationship between BDNF genotype and cognition in mTBI may differ from that in healthy individuals, where the presence of the met allele may actually promote improved cognitive outcome under the pathological conditions following a head injury. Although BDNF genotype may not be a sufficient biomarker for long-term TBI outcome in isolation, future research on chronic TBI in individuals with different BDNF genotypes may reveal important differences in brain morphology and connectivity.

Conclusion.

Given the necessity for an objective method of identifying and characterizing TBI, an extensive body of research evaluating putative biomarkers for TBI has developed over the past decade. Biomarkers of chronic mTBI, specifically, are important targets within this division of research given that they may help illuminate the underlying pathological processes that unfold over time after the initial stage of injury. Such information is not only critical for elucidating the poorly understood processes leading to poor long-term outcomes associated with milder forms of head injury, but it may furthermore help to identify possible targets for prevention or treatment of PCS and neurodegenerative diseases. Several potentially strong candidates have been identified in this review, most of which are associated with and/or reflective of both chronic vascular dysfunction (e.g., BBB breakdown) and neuroinflammation. This supports the notion that these mechanisms are likely involved with acute pathology following TBI, and possibly the chronic pathology in response to secondary injury. Importantly, however, most of these biomarkers have only been investigated in moderate-to-severe TBI populations.

Thus, while the available literature suggests that several pro- and anti-inflammatory cytokines may serve as useful biomarkers of acute and chronic phase moderate-to-severe TBI, the utility of these biomarkers for mTBI remains unclear.

There are several additional caveats to the use of inflammatory cytokines as biomarkers of acute and chronic phase TBI. First, while many of the described markers sensitive to acute and chronic phase moderate-to-severe TBI, most of them lack specificity. This is largely because inflammatory cytokines measured in blood serum or plasma are largely non-specific to central inflammation (as peripheral injuries can also cause alterations in these markers). While CSF levels of these markers seem to be a superior measurement method for central inflammation, at least in terms of specificity, additional challenges exist with this respect in the TBI population due to the prevalence of BBB dysfunction. That is, the BBB dysfunction may act as a confounder for CSF concentration of inflammatory proteins. Importantly, however, while there exists clear limitations to the use of inflammatory cytokines as biomarkers for acute and chronic phase TBI, it should be noted that many of these challenges apply to most other potential fluid biomarkers. This highlights the need for careful consideration of the medium-specific sensitivity and specificity of all potential biomarkers for TBI, and emphasizes the need for future research aimed at clarifying the diagnostic and prognostic value of inflammatory biomarkers for different subclasses and phases of neurotrauma.

Future Perspective.

While the present review indicates the utility of certain biomarkers for acute and chronic phase in moderate-to-severe TBI, there is a marked apparent lack of studies available related to these topics in mTBI samples, although research is increasing in this

area. To date, several recent studies have demonstrated chronic vascular dysfunction in mTBI, supporting the notion that chronic phase injury can exist even in mild forms of neurotrauma (15, 27-30). While notably less research has been conducted in the arena of chronic inflammation in remote mTBI, future endeavors to explore the presence of chronic inflammation in mTBI should be prioritized given the empirical support for the presence of these processed in moderate-to-severe TBI. Indeed, such research may provide findings that not only critically aid in the identification of individuals at high risk for developing poor long-term outcomes following mTBI, but may also inform the development of targeted interventions which may reduce persisting symptomatology. Additionally, given that many of the reviewed biomarkers have limited utility when used in isolation, a multi-biomarker approach should thus be considered in future research, as the combined characteristics of the above-mentioned biomarkers have the potential to address many of these failures of individual biomarkers in the prediction of outcome in head injured populations. Moreover, integrating multi-modal biomarker approaches (e.g., fluid biochemical assays, neuroimaging, electrophysiological measures) may be particularly promising, given that different biomarker methods may provide varied methodological advantages and disadvantages with respect to acute and chronic phase TBI sensitivity and specificity. Lastly, since most of the discussed biomarkers have only been studied in the context of moderate and severe TBI during the acute phase of injury, future research is needed to test the utility of these biomarkers in the setting of the chronic effects of mild TBI.

Executive summary.

- **Introduction:** Growing evidence suggests that TBI—even milder forms—should be conceptualized as a dynamic process that can affect brain health, directly and indirectly, several years after the initial insult. Thus, TBI research has begun to identify effective biomarkers for both the acute (i.e., primary injury sustained from the initial traumatic force) and chronic (secondary pathological processes that unfold after the initial brain injury that cause long-term changes to brain structure and function) phases of injury.
- **Characteristics of TBI and Tissue Injury Mechanisms:** There are several different ways in which TBI can be classified, including (1) the source of force causing the injury; (2) injury severity; and (3) mechanism of brain tissue damage. Despite these differences, research to-date suggests that certain primary and secondary pathological mechanisms are common across closed (non-penetrating) TBI types.
- **Vascular Dysfunction and TBI Secondary Injury:** The presence of chronic vascular dysfunction and neuroinflammation may characterize the chronic phase TBI, and indeed be responsible for the poor long-term outcomes reported in some individuals.
- **Biomarkers of Acute and Chronic Pathological Processes Following TBI:** Various inflammatory cytokines (i.e., TNF, IL-1B, IL-6, IL-8, IL-10) have been studied in acute and chronic phase TBI. These studies have evaluated the diagnostic and prognostic sensitivity and specificity of these markers. While not

frequently discussed in conjunction with these biomarkers, genetic factors should be considered when evaluating the utility of acute and chronic biomarkers of TBI.

- **Conclusion and Future Perspectives:** Several inflammatory cytokines appear to be sensitive diagnostic biomarkers for acute and chronic phase TBI, although most of the extant literature focuses on moderate-to-severe samples. Many of these markers, however, lack specificity to TBI, and furthermore have mixed prognostic value for injury outcome. Given the lack of research on this topic in mTBI samples, future studies should aim to explore the presence of these pathological processes in acute and chronic phase mTBI, in addition to validating multi-biomarker approaches to improve diagnostic specificity of TBI and long-term prognostic predictive value for these biomarkers across the injury severity spectrum.

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Research Submission

Neuropsychiatric Predictors of Post-Injury Headache After Mild-Moderate Traumatic Brain Injury in Veterans

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Objectives.—To determine differences in neuropsychiatric complaints between Veterans with mild to moderate traumatic brain injury (TBI), with and without headache, compared with Veteran controls, and to identify neuropsychiatric predictors of headache severity.

Background.—Mild to moderate TBI is a common occurrence in Veterans, and is frequently associated with complaints of headache. Neuropsychiatric complaints are also common among individuals who have sustained head injury, although the relationship between these factors and headache after injury is unclear. Research is needed to comprehensively determine differences between individuals with mild to moderate traumatic brain injury who differ with respect to headache, and which injury, psychological, or sleep and fatigue factors predict headache severity.

Methods.—A cross-sectional study compared 85 Veterans in three groups (positive for TBI and headache, positive for TBI without significant headache, and a control group) on a set of injury characteristics and neuropsychiatric variables. Correlates of headache severity were examined, and a regression model was used to identify significant independent predictors of headache severity.

Results.—Individuals with mild to moderate TBI and headache endorsed significantly greater neuropsychiatric symptoms than participants in the other groups ($\eta_p^2 = .23-.36$) Neuropsychiatric complaints, as well as presence of posttraumatic amnesia, were correlated with headache in the subsample with TBI ($rs = .44-.57$). When entering all predictors into a regression model, only fatigue represented a significant independent predictor of headache severity ($\beta = .59$, $R^2 = .35$).

Conclusions.—Rather than being a global risk factor, mild to moderate TBI was associated with poorer mental health outcomes, particularly for those who endorse headache. Findings underscore the possibility that Veterans with history of TBI who present with complaints of headache may represent a particularly vulnerable subgroup. Additionally, our findings suggest that clinical outcomes may be improved in those with neurotrauma by incorporating a focus on fatigue in treatment.

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Key words: traumatic brain injury, headache, post-traumatic headache, post-injury headache

Abbreviations: ANOVA analysis of variance, AOC alteration of consciousness, BAI Beck Anxiety Inventory, BDI-II Beck Depression Inventory, II edition, DSM-IV Diagnostic and Statistical Manual of Mental Disorders, 4th edition, LOC loss of consciousness, MFIS Modified Fatigue Impact Scale, mmTBI mild to moderate traumatic brain injury, NSI Neurobehavioral Symptom Inventory, OEF Operation Enduring Freedom, OIF Operation Iraqi Freedom, PCL Posttraumatic stress checklist-military version, PCS postconcussive symptoms, PSQI Pittsburgh Sleep Quality Index, PTA posttraumatic amnesia, PTH post injury headache, PTSD posttraumatic stress disorder, TBI traumatic brain injury, TBI/PTH- group with TBI and without PTH, TBI/PTH+ group with TBI and PTH, VC veteran control group

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INTRODUCTION

Traumatic brain injury (TBI) has been deemed the "signature injury" of recent military operations due to the high rates (20% or more) of individuals experiencing head injury during military service.[1,2] Headache is one of the most common symptoms following mild to moderate TBI (mmTBI),[3-6] with prevalence ranging from 32% to 91%[1,7] (for reviews see refs. 8,9). Headache after TBI (ie, post-traumatic headache; PTH) is associated with significant disability and functional impairment in military and veteran populations (eg, low return-to-duty rates[9-12]). Given the high prevalence, disability, and costs associated with PTH in military personnel, it is critical to better understand factors associated with the presence and severity of this condition in Veterans.

The characteristics of PTH and underlying mechanisms by which a concussive injury may lead to new or exacerbated headache are poorly understood. Headache specifically occurring or worsening immediately after TBI is often classified as a unique headache syndrome that may have a partially distinct etiology due to biomechanical forces on the musculoskeletal system and resultant neural changes occurring during or shortly after head injury.[13,14] However, inconsistency of associations between headache and indicators of brain damage suggest that these mechanisms may not account for headache in all (or even most) cases.[15] For example, some studies have found a positive relationship between PTH and loss of consciousness (LOC), an index of TBI severity,[16] while other studies have shown that greater LOC is *inversely* associated with PTH.[17,18] PTH may alternatively represent an exacerbation of a primary headache disorder (ie, most predominantly, tension-type or migraine-type headache) related to stress from the head injury itself, and some researchers suggest that PTH mechanisms may be similar to other headaches that occur in individuals without TBI.[9]

While the association of PTH with injury characteristics is debatable, several studies have shown that psychological and behavioral health symptoms contribute to the clinical presentation of headache after mmTBI. Higher rates of PTSD, anxiety, and depression have been observed in military personnel with both mild TBI and PTH compared to those with mild TBI and no PTH[19] (see also ref. 20 for similar data in civilians). Moreover, PTSD symptoms are associated with greater PTH severity,[16] and comorbid PTSD is associated with greater self-reported disability in military personnel with PTH.[21] However, a significant limitation of most prior studies is the lack of a control group with no history of TBI, which limits exploration of connections between mmTBI, PTH, and psychological symptoms. Based on the body of research showing that neurotrauma is associated with[11] and prospectively predictive of psychopathology,[22] one might predict that mmTBI is ubiquitously associated with greater psychiatric symptoms regardless of PTH status, or that PTH could be a manifestation of higher levels of general emotional distress. Conversely, it is possible that individuals with mmTBI, but without PTH, represent a particularly resilient group of individuals who demonstrate low levels of psychiatric distress. To date, only one published study examined groups separately to describe rates of PTSD in those with mild TBI, with and without PTH, compared with no-TBI controls. Defrin et al[23] found that greater PTSD severity

characterized only the mild TBI with PTH group, suggesting that elevated rates of psychopathology observed in mild TBI samples may be specific to those reporting headaches (see also ref. 24 for similar findings in individuals across categories of TBI severity). Taken together, psychological symptoms appear to be associated with PTH, although research examining PTH in the context of psychological functioning more broadly (beyond PTSD) and assessing associations between TBI status, PTH, and symptoms is critically needed, particularly within military samples that are so commonly impacted by TBI and its physical and mental health sequelae.

In addition to psychopathology, sleep and fatigue problems frequently occur in the wake of mmTBI, and they may impact or be impacted by PTH. Difficulty with sleep, including delayed sleep onset, disrupted sleep, and poor sleep quality, are common postconcussive symptoms (PCS).[25-27] Moreover, data suggest that sleep disturbance is a key factor implicated in how TBI confers risk for later psychological symptoms.[28] Fatigue, which may be related to but does not fully correspond with sleep difficulties,[29,30] is also a prevalent symptom for individuals with mmTBI,[31-36] and may reflect trauma-induced changes in neurotransmission required for modulating arousal.[27] Headache has known associations with sleep problems and fatigue.[37-41] Moreover, sleep disturbance and headache have been shown to be related in mmTBI samples[16,32]), as have fatigue and pain more generally.[42] However, associations between sleep complaints, fatigue, and headache taking into account overlapping symptoms, such as PTSD and anxiety, have yet to be thoroughly examined in Veterans.

In summary, neuropsychiatric complaints are common in Veterans who have sustained mmTBI(s); however, their relationship to PTH occurrence or severity is unclear. Further research is needed to comprehensively characterize differences between individuals with mmTBI who differ on PTH (as compared to those without mmTBI), and investigate specific injury, psychological, and/or sleep and fatigue predictors of PTH severity. In order to address these questions, the current study used a retrospective cross-sectional design in order to: (1) compare individuals across the following three groups – mmTBI with PTH (TBI/PTH+), mmTBI without PTH (TBI/PTH-), and a no-TBI Veteran control group (VC) – on a comprehensive set of psychological functioning variables (ie, PTSD, depression, general trait anxiety), sleep quality and fatigue, as well as TBI-related injury characteristics; and (2) explore correlates of PTH severity and the independent contribution of associated factors in predicting headache severity within mmTBI. Based on prior literature, we predicted that individuals in the TBI/PTH+ group would endorse more neuropsychiatric symptoms than those in the TBI/PTH- group, who would, in turn, endorse more symptomatology than the VC group. We predicted that neuropsychiatric symptoms would be associated with greater PTH severity.

METHODS

Participants.—Participants were 52 Operation Enduring Freedom (OEF)/Operation Iraqi Freedom (OIF)/Operation New Dawn (OND)/Persian Gulf Veterans with mmTBI (n = 34 with moderate to severe PTH; n = 18 with no or mild PTH) and 32 OEF/OIF/OND/Persian Gulf Veterans without a history of TBI who participated in a larger study on neuropsychological and neurological correlates of TBI in Veterans. All data were collected at the VA San Diego Healthcare System (VASDHS) from September 2010 to September 2014. Since the current analyses represent a retrospective subsample from a larger study, the sample size was determined based on logistical considerations (ie, participants recruited from the parent study). Potential participants were recruited for the parent study through outpatient TBI treatment clinics at VASDHS using IRB-approved recruitment postings. The VC group was recruited through study advertisements posted throughout VASDHS. Eligibility to participate was determined via an initial screening interview, described below. Other questionnaire data from a portion of participants in this study were also reported by Schiehser et al[43,44] in studies examining the psychometric properties of the MFIS and the

relationship between quality of life and post-concussive symptoms.

TBI history was determined using a semi-structured interview that involved a series of open-ended questions and prompts modeled on the VA's semistructured clinical interview for TBI identification. The interview assessed elements of head trauma events including the number of head injuries sustained, and severity-related data for each injury (eg, duration of LOC, alteration of consciousness [AOC], and posttraumatic amnesia [PTA]). TBI was defined by the VA/DoD Clinical Practice Guideline for Management of Concussion/Mild TBI[45] as "a traumatically induced structural injury and/or physiologic disruption of brain function as a result of an external force that is indicated by new onset or worsening of at least *one* of the following: (1) any period of LOC; (2) any loss of memory for events immediately before or after the accident (PTA); (3) any alteration in mental state at the time of the accident (AOC); or (4) neurological deficits that may or may not be transient." Categorization of TBI severity was based on the "worst" or "most significant" TBI reported. Forty-two participants (81% of TBI sample) met criteria for *mild* TBI, defined by (a) an initial LOC of less than 30 minutes, (b) AOC up to 24 hours, and/or (c) PTA of less than 24 hours. Ten participants (19% of TBI sample) met criteria for *moderate* TBI, defined by (a) an initial LOC of greater than 30 minutes and less than 24 hours, (b) AOC greater than 24 hours, and/or (c) PTA greater than 24 hours but less than 7 days. The TBI/PTH+ and TBI/PTH− groups did not differ in terms of TBI severity ($P > .7$). Individuals in the VC group had no history of TBI; however, they could have other mental or physical health disorders so long as they met the inclusion and exclusion criteria described below.

Exclusion criteria for this study included (1) any current (within 30 days) substance or alcohol abuse/dependence according to the Diagnostic and Statistical Manual of Mental Disorders (4th edition; *DSM-IV*[46]) criteria; (2) history of a neurological or metabolic disorder or disease known to affect the central nervous system (other than migraine and TBI for the TBI group); (3) a history of bipolar disorder, schizophrenia or other psychotic disorders; and (4) history of severe TBI defined by an initial LOC >24 hours and/or PTA >7 days. Inclusion in the TBI group required a most significant TBI of mild to moderate severity at age 18 or older. All participants provided written informed consent, and all procedures complied with the local VA institutional review board. All authors listed on this manuscript had access to the data used in this study.

Materials.—Participants completed a battery of self-report measures to assess psychological, sleep, and fatigue complaints. A demographics form that included questions regarding basic socioeconomic, demographic, and military experience variables (eg, history of combat exposure) was administered as part of this battery. Individual measures grouped by symptom(s) are described below.

Headache. The mmTBI participants were split into one of two groups: TBI with headache (TBI/PTH+) or TBI without significant headaches (TBI/PTH−) based on their scores on the neurobehavioral symptom inventory (NSI)[47] headache item (#4). The NSI is a 22-item self-report questionnaire widely used for evaluation of PCS by the Department of Defense and in the VA as part of comprehensive TBI evaluation. Items ask the individual to rate each symptom (including cognitive, emotional, and somatic domains) for frequency and disruption of daily activities. Factor analytic studies suggest that the items of the NSI can be organized into somatosensory, affective, cognitive, and vestibular categories. For the headache item, respondents were asked to rate how much headaches have disturbed them since their injury on a Likert scale of 0 (none; rarely ever present/not a problem at all) to 4 (very severe; almost always present/impairs performance at work, school, or home/probably cannot function without help). Individuals who scored a 0 (none; n = 8) or 1 (mild; n = 10) on the NSI were grouped as TBI/PTH−, while those with scores 2 (moderate; $n = 17$) or higher (n = 17) were grouped as TBI/PTH+.

Neuropsychiatric Symptoms.—*Anxiety.*—Anxiety was assessed using the Beck Anxiety Inventory (BAI[48]). The BAI is a 21-item self-report measure of anxiety-related physiological arousal with items

Table 1.—Sample Characteristics

Variable	TBI/PTH+ (N =34)	TBI/PTH− (N = 18)	VC (N = 32)
Mean Age (*SD*)	31.8 (6.4)	33.7 (7.3)	32.5 (8.1)
% Female**	11.8	11.1	43.7
Ethnicity category*			
Caucasian	16	6	25
Black	2	3	0
Asian	4	3	1
Hispanic	10	6	4
Other/Biracial/Unknown	2	0	2
Mean education (SD)	14.1 (1.3)	14.6 (1.9)	14.9 (2.0)
% with combat exposure**	76.5	61.1	37.5
% Mild TBI	79.4	83.3	n/a
% Experiencing LOC	64.7	61.1	n/a
% Experiencing PTA	64.7	38.9*	n/a
Mean number of TBIs (SD)	3.0 (1.7)	2.1 (1.4)	n/a
Mean months since TBI	75.3 (41.9)	82.5 (36.5)	n/a
Mean PCL (SD)***	48.3 (17.3)$^{+}$	32.7 (17.3)‡	21.9 (8.5)
Mean BDI-II (SD)***	23.4 (12.5)$^{++}$	12.1 (11.8)‡	5.8 (11.0)
Mean BAI (SD)***	14.4 (9.9)$^{++}$	7.8 (9.4)	2.7 (4.6)
Mean MFIS (SD)***	46.1 (16.7)$^{++}$	24.8 (21.4)§	14.4 (16.2)
Mean PSQI (SD)***	12.5 (3.6)$^{++}$	7.9 (4.4)§	5.4 (3.6)
Mean NSI headache item	2.7 (.8)	0.6 (0.5)	n/a
Mean NSI total score	38.7 (13.7)	15.7 (16.9)§	n/a
NSI somatic factor	10.4 (5.0)	3.4 (4.2)§	n/a
NSI affective factor	13.2 (5.5)	5.6 (6.5)§	n/a
NSI cognitive factor	8.8 (4.0)	3.9 (4.2)§	n/a
NSI vestibular factor	3.7 (2.3)	1.3 (1.7)§	

*$P < .05$; **$P < .01$; ***$P < .001$.
Omnibus group differences: Bonferroni-corrected pairwise comparison differences between VC and other groups:$^{+}P <$ $.01^{++}P < .001$. Pairwise comparison differences between PTH+/−: $^{\ddagger}P < .01$, $^{\S}P < .001$
Note: Two individuals missing LOC and PTA data were excluded from analyses comparing TBI/PTH+ and TBI/PTH- groups on these variables and from correlation and regression analysis in Tables 2-3.
LOC = loss or alteration of consciousness; PTA = posttraumatic amnesia; PCL = posttraumatic symptoms checklist; BDI-II = Beck Depression Inventory-II; BAI = Beck Anxiety Inventory; MFIS = Modified Fatigue Impact Scale; PSQI = Pittsburgh Sleep Quality Index; NSI = Neurobehavioral Symptom Inventory; SD = standard deviation.

scored on a one to four Likert-type scale. Items are summed to create a total score with a range of 0-63. This measure possesses adequate psychometric characteristics.[48,49]

Depression.—To assess symptoms of depression, the Beck Depression Inventory-II (BDI-II)[50] was administered. The BDI-II includes 21 items assessing symptoms over the previous two weeks. Items are scored on a scale of zero to three with a range from 0 to 63. The BDI-II is a reliable and well-validated measure of depressive symptoms[50]).

PTSD.—The PTSD Checklist-Military version (PCL)[51] was administered to assess PTSD symptoms. The PCL is a 17-item measure consisting of items that correspond to distress associated with PTSD symptoms outlined in the *DSM-IV*. Items are rated on a scale from 1 (not at all bothersome) to 5 (extremely bothersome) and summed to create a total score. This measure has demonstrated adequate psychometrics properties.[52]

Sleep.—Pittsburgh Sleep Quality Index (PSQI)[53] was administered to assess sleep. The PSQI is a psychometrically sound self-rated questionnaire that queries sleep quality and disturbances over a 1-month interval. Seven component scores (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction) are derived from 19 individual items. The sum of scores for these seven components yields one global score.

Fatigue.—The Modified Fatigue Impact Scale (MFIS; predicated on the FIS)[54] measures the impact of fatigue on functioning by having participants rate how often fatigue has affected 21 functions during the past four weeks using a 0 (never) to 4 (almost always) point scale. Total scores range from 0 to 84, with higher scores indicating greater impact of fatigue. Schiehser et al[43] found that the MFIS is a valid measure of fatigue in mmTBI.

Statistical Analyses.—Analysis of variance (ANOVA) was used to examine differences in continuous demographic and injury characteristics between the groups. Differences in gender, ethnicity, and combat exposure distribution between groups were analyzed with chi-square tests. Analyses of covariance (ANCOVA), with gender, ethnicity, and self-reported combat exposure (yes/no) serving as covariates, were employed in order to assess the group differences on neuropsychiatric variables. Partial eta-squared is reported to show the magnitude of effects for the ANCOVA models, and reflects the amount of variance accounted for by each variable, excluding variance accounted for by the other predictors. Correlational analyses were conducted to evaluate the associations of depression, PTSD, fatigue, sleep difficulty, and injury characteristics with PTH within the mmTBI sample. Multiple linear regressions were fit with the total score of the headache variable from the NSI serving as the dependent variable, and variables that were significantly correlated with headache severity serving as predictors. Analyses were repeated including only participants with mild TBI; because the pattern of results remained the sample all participants were retained in the final analyses reported herein. Bonferroni adjusted a critical *P*-values $< .01$, were applied to correct for multiple comparisons when appropriate as detailed below.

RESULTS

Demographic and TBI-Related Variables.—The TBI/PTH+, TBI/PTH-, and VC groups did not significantly differ in age or education (Ps $> .16$). The VC group had a higher proportion of women ($\chi^2 = 11.33$; $P = .003$), non-minority participants ($\chi^2 = 16.78$; $P = .03$) and less combat exposure ($\chi^2 = 10.37$; $P = .01$) compared to the groups with TBI. A higher proportion of individuals in the TBI/PTH+ group endorsed post-traumatic amnesia (PTA) than in the TBI/PTH- group, ($\chi^2 = 4.22$; $P = .04$). No significant differences were found between groups with mmTBI on other injury-related characteristics (ie, total number of TBIs, months since TBI, number of participants experiencing LOC, all $Ps > .07$). Table 1 presents descriptive information for all psychological and injury-related variables.

Group Differences on Neuropsychiatric Symptoms.—Controlling for gender, ethnicity, and combat exposure, groups significantly differed on measures of PTSD, $F(2, 75) = 18.98$, $P < .001$, $\eta_p^2 = .34$, depression, $F(2, 75) = 16.15$, $P < .001$, $\eta_p = .30$, and anxiety, $F(2, 75) = 11.30$, $P < .001$, $\eta_p^2 = .23$. Similarly, groups differed on measures of sleep quality, $F(2, 75) = 20.55$, $p < .001$, $\eta_p^2 = .35$, and fatigue, $F(2, 75) = 20.97$, $p < .001$, $\eta_p^2 = .36$. Individual Bonferroni-corrected contrasts ($P_{crit} < .01$) revealed that the TBI/PTH+ endorsed greater levels of all emotional/fatigue/sleep symptoms compared to both the TBI/PTH− and VC groups (with the exception of BAI), while TBI/PTH− and VC groups did not significantly differ from each other (see Table 1).

Predictors of Headache Severity Following TBI.—Psychological symptoms, sleep and fatigue complaints, and greater PTA were each positively associated with headache severity in mmTBI (+/-PTH) participants (see Table 2). Stepwise multiple linear regression analysis was then conducted with all variables that were significantly correlated with the NSI headache item in the mmTBI group (ie, PCL, BAI, BDI-II, PSQI, MFIS, and PTA scores) and entered as predictors of post-TBI headache severity (Table 3). Results revealed that only the MFIS total score was a significant predictor of headache severity in the mmTBI group ($B = .03$, $SE = 01$, $P < .001$, $R^2 = .35$).

CONCLUSION

Consistent with study hypotheses, results revealed that individuals with a history of mmTBI and current post-injury headache reported higher levels of PTSD, depression, and anxiety compared to

Table 2.—Bivariate Correlations Between Demographic Variables, Anxiety, Depression, PTSD, and NSI Headache Severity in mmTBI (n = 52)

Measure	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Gender	1.00													
2. Age	.02	1.0												
3. Education	.17	.27	1.00											
4. Ethnicity	.28*	.34*	.18	1.00										
5. Combat exposure	−.17	.20	.06	−.14	1.00									
6. BDI-II	−.004	.01	−.18	−.01	−.04	1.00								
7. BAI	.06	.06	−.04	−.05	.07	.64***	1.00							
8. PCL	−.16	.05	−.06	−.12	.15	.78***	.76***	1.00						
9. PSQI	−.10	.01	−.16	−.24	.15	.48***	.40**	.52***	1.00					
10. MFIS	.09	.16	−.07	−.01	.11	.79***	.68***	.71***	.64***	1.00				
11. LOC	.14	.04	.05	.08	−.07	.15	.09	.09	−.09	.07	1.00			
12. # TBIs	−.08	.19	.08	.03	.34*	.10	.30*	.15	.19	.24	.13	1.00		
13. PTA	.07	.20	−.02	.11	−.03	.23	.25	.25	.30*	.42**	.22	.11	1.00	
14. NSI headache	−.03	−.07	−.08	−.04	.25	.46**	.44***	.52***	.51***	.57***	.08	.24	.30**	1.00

*$P < .05$; **$P < .01$; ***$P < .001$.
Note. Two individuals missing LOC and PTA data were excluded from analyses correlating headache with these variables.
PCL = Posttraumatic Stress Checklist; BDI-II = Beck Depression Inventory II; BAI = Beck Anxiety Inventory;
PSQI = Pittsburgh Sleep Quality Index; MFIS= Modified Fatigue Impact Score; LOC = loss or alteration of consciousness;
PTA = post-traumatic amnesia; NSI = Neurobehavioral Symptom Inventory.

both mmTBI Veterans without significant PTH and Veteran controls without a history of TBI. These results are consistent with those of Defrin et al,[23] which showed that individuals with co-occurring mild TBI and headache endorsed greater symptoms of PTSD than those not reporting headache. They also converge with studies that have shown generally greater rates of psychopathology in Veterans with headache compared to those without headaches,[55] as well as findings demonstrating that PTSD symptoms are associated with headache severity, at least in the context of acute military head trauma.[16] Our results extend these findings by further indicating that psychopathology in general (not just PTSD) is problematic in Veterans with mmTBI, several years or more after injury. Surprisingly, mmTBI Veterans without significant PTH and Veteran controls did not significantly differ in their symptom profiles. Taken together, our results highlight the importance of PTH in determining the extent to which TBI has a detrimental impact on and complicates psychological outcomes; that is, increased rates of psychopathology may *not* characterize *all* individuals with TBI, but rather they may co-occur within a vulnerable subgroup endorsing higher levels of PTH.

Table 3.—Stepwise Regression Predicting NSI Headache Severity From Anxiety, Depression, PTSD, Sleep, and Fatigue in mmTBI (n = 50)

Included Predictor	β	t	*P*
MFIS	0.59	5.1	< .001
Excluded Predictors	β	t	*P*
BDI-II	−.05	−0.2	.8
BAI	−0.01	−0.03	.9
PTSD	0.1	0.6	.6
PSQI	0.2	1.6	.1
PTA	0.1	0.4	.7

Note: β and *P* estimates for excluded predictors reflect the value if variables were to be entered into the regression model.

While this study cannot determine how etiological processes ultimately culminate in the co-occurrence of headache and mental health symptoms, it is possible that experiencing headache pain following TBI may increase psychological symptoms due to associated functional impairments (eg, increased depression in

response to difficulty in maintaining work or social functioning) or cognitive factors (eg, headache serves as a reminder of the injury or traumatic event). Alternatively, psychopathology symptoms existing prior to or soon after head injury may be predisposing vulnerability factors for headache development following TBI.[19] This vulnerability could be conferred by symptoms that are inherent in psychological disorders and also maladaptive in pain management (eg, inactivity, muscle tension[56]). Shared vulnerabilities at the biological (eg, genetic[55]) or psychological (eg, anxiety and injury/illness sensitivity[57]) level could also account for observed relationships. As this study is cross-sectional in nature, the current data cannot address the temporal sequence in which individuals develop headache and psychopathology, but suggest that this question will be important to explore in future research.

Findings of this study also demonstrate that groups differed on measures of fatigue and sleep, with those individuals with higher levels of PTH endorsing more complaints that those in the other groups. Data are consistent with the extant literature suggesting that insomnia is associated with PTH.[16] Our results are also broadly consistent with earlier studies showing that those with headache experience fatigue at greater rates,[58] and that individuals with chronic headache perceive fatigue as more severe than those without headache.[59] As with the findings on psychopathology, data suggest that sleep and fatigue complaints may be particularly problematic for those with co-occurring headache, and further research is needed to determine why individuals with significant PTH would experience poorer sleep and fatigue. As stated earlier, causal directionality cannot be determined in this cross-sectional study; however, a number of hypotheses are plausible. For example, headache may interfere directly with sleep quality via pain-related arousal during sleep,[60] which may also result in more sleep complaints and increased fatigue. Alternatively, since sleep disturbance detrimentally alters pain perception, threshold, and pain inhibition, it is possible that sleep problems may lead to increased PTH via disruptions in pain processing.[16,61,62] It is also possible that a bidirectional relationship between headache and sleep and/or fatigue symptoms exists, incorporating these and other pathways[38] or that a third variable (eg, central or obstructive sleep apneas that are common in TBI) may account in part for the observed relationships.[39,63-65] Importantly, sleep and fatigue are not entirely overlapping constructs, and the associations between headache and fatigue may represent distinct associations that are independent of sleep disruption. For example, the experience of pain may lead to the feeling of fatigue[40] or vice versa. Future research is needed to better understand the etiology of fatigue and its relationship to sleep and psychological factors in those with history of TBI.

In mmTBI, PTH severity was associated with all measured neuropsychiatric factors, yet minimally associated with TBI characteristics or demographics, with the exception of PTA. In contrast to our findings, a number of studies have found no association between category of TBI severity – indexed by PTA duration – and headache.[7,66,67] The substantial heterogeneity across study methods, including the time lapse between injury headache assessment, inclusion criteria and TBI criteria, population, or assessment type (ie, presence/absence of PTA versus duration, combining LOC and PTA into a single "severity" variable) may account for discrepant findings. Understanding how factors leading to PTA contribute to subsequent persistent headache is in need of further empirical attention. Importantly, in the current study, the relationship between PTA and PTH no longer reached the level of statistical significance when controlling for other factors, suggesting that shared variance with other factors may have been responsible for the correlation.

When all significant symptom measures were entered simultaneously, fatigue emerged as the only significant predictor of PTH severity. The unique contribution of fatigue over and above clinical conditions that co-occur with both fatigue and headache (eg, depression) and injury factors, as well as sleep disturbance, highlights the importance of considering this type of symptom in relation to headache complaints. Fatigue and headaches are often indexed as the most common symptoms following TBI[31-33] and our findings further underscore the close relationship between these two symptoms. Evidence suggests a close link between pain and

fatigue and that these symptoms may be modulated by the central nervous system[68]. It is possible that TBI disrupts this system and thereby induces fatigue and pain, although to what degree these impact and/or induce one another as well as why it appears to only be relevant in a particular subgroup of TBI remains unknown.

There are some limitations of this study that should be noted. First, TBI assessments were conducted via self-report, which is susceptible to potential biases. However, this is largely unavoidable for this population, as medical records and third-party observations for military personnel are often unavailable. In addition, PTH was measured using a retrospective self-reported item. Since our interest in headache severity was specific to those with TBI, headache was not comprehensively assessed in the VC group. Thus, we cannot establish differences in headache severity between the VC and other groups. Also, it is possible that different types of headaches were represented in the PTH group, including pre-existing migraine or tension-type headache, or medication overuse headache due to heavy reliance on analgesics or caffeine use. Future studies would benefit from a more comprehensive assessment of headache (including type and correspondence to the stricter definition of PTH outlined by the International Headache Classification) and replication in samples with other types of headache. Our data collection did not include a measure assessing compensation seeking for injuries. Thus, we cannot address whether secondary gain is a potential factor accounting for greater distress reported in the TBI/PTH+ group. Moreover, the current study categorized individuals with no or mild headache in the same group (TBI/PTH-). However, it is possible that there are important clinical differences between individuals who experience some headache, even if mild, and those who experience no headache at all. Thus, future research comparing a larger group of individuals with no and mild headache separately could provide important information to distinguish these groups. Data were collected cross-sectionally and therefore conclusions regarding the directionality of relationships cannot be obtained, and we cannot determine what specifically drives the increased distress in the PTH group (eg, depression increasing PTSD or vice versa) given that symptoms were elevated across multiple categories. Future studies should examine these questions, and should also examine the relative contribution of fatigue and psychopathology to headache prospectively over time. In spite of existing limitations, these data provide initial evidence pointing to the importance of headache in individuals with TBI given the higher rates of distress in this group. Because the study sample was a specific population (Veterans), results may not generalize to other groups.

Findings of this study showed that PTH is closely associated with neuropsychiatric symptoms, most especially fatigue, in Veterans with history of mm TBI. Our results provide further evidence that PTH complicates outcomes in the context of head trauma, and they provide information that may be useful for the development of targeted treatments and management of TBI patients. Indeed, results strongly suggest that treatments that focus on fatigue may be more critical for those who endorse PTH, and they underscore the positive utility related to addressing and treating PTH and fatigue to improve clinical outcomes in individuals who have sustained neurotrauma. Incorporating sleep and psychological factors may also prove beneficial. In general, the high co-occurrence of PTH with neuropsychiatric symptoms underscores the need for comprehensive assessment and continued treatment research. Such targeted treatment could improve quality of life, as recent work has suggested that fatigue is one of the most important symptoms associated with poor quality of life in mild-moderate TBI.[44] Taken together, results highlight the importance of understanding heterogeneous subgroups of individuals with TBI who experience greater levels of distress, and have clinical implications for how to address treatment for individuals with post-injury headache.

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Dynamic association between perfusion and white matter integrity across time since injury in Veterans with history of TBI

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ABSTRACT

Objective

Cerebral blood flow (CBF) plays a critical role in the maintenance of neuronal integrity, and CBF alterations have been linked to deleterious white matter changes. Although both CBF and white matter microstructural alterations have been observed within the context of traumatic brain injury (TBI), the degree to which these pathological changes relate to one another and whether this association is altered by time since injury have not been examined. The current study therefore sought to clarify associations between resting CBF and white matter microstructure post-TBI.

Methods

37 veterans with history of mild or moderate TBI (mmTBI) underwent neuroimaging and completed health and psychiatric symptom questionnaires. Resting CBF was measured with multiphase pseudocontinuous arterial spin labeling (MPPCASL), and white matter microstructural integrity was measured with diffusion tensor imaging (DTI). The cingulate cortex and cingulum bundle were selected as a priori regions of interest for the ASL and DTI data, respectively, given the known vulnerability of these regions to TBI.

Results

Regression analyses controlling for age, sex, and posttraumatic stress disorder (PTSD) symptoms revealed a significant time since injury × resting CBF interaction for the left cingulum ($p < 0.005$). Decreased CBF was significantly associated with reduced cingulum fractional anisotropy (FA) in the chronic phase; however, no such association was observed for participants with less remote TBI.

Conclusions

Our results showed that reduced CBF was associated with poorer white matter integrity in those who were further removed from their brain injury. Findings provide preliminary evidence of a possible dynamic association between CBF and white matter microstructure that warrants additional consideration within the context of the negative long-term clinical outcomes frequently observed in those with history of TBI. Additional cross-disciplinary studies integrating multiple imaging modalities (e.g., DTI, ASL) and refined neuropsychiatric assessment are needed to better understand the nature, temporal course, and dynamic association between brain changes and clinical outcomes post-injury.

1. Introduction

Traumatic brain injury (TBI) has come to be known as the predominant injury of U.S. Veterans returning from the recent wars in Iraq and Afghanistan (Hoge et al., 2008). Of the nearly two million military service members that have been deployed since the beginning of these wars, estimates suggest that an astounding 15–25% of these individuals have sustained at least one TBI during deployment (Fortier et al., 2014; Hoge et al., 2008; Terrio et al., 2011; Warden, 2006). The vast majority of these injuries can be classified as either mild or moderate (Defense and Veterans Brain Injury Center, 2016), and are often the direct result of either blunt-force (i.e., direct blow to the head) or blast-related (i.e., pressure wave from an explosive device) trauma. While most Veterans who experience mild neurotrauma do not require immediate or emergency medical care at the time of injury, a host of troubling cognitive (e.g., executive dysfunction, attention and memory deficits) (Combs et al., 2015; Vanderploeg, Curtiss & Belanger, 2005), post-concussive (e.g., headaches, dizziness, fatigue) (King et al., 2012; Lippa, Pastoerk, Benge, & Thornton, 2010;), and psychiatric symptoms (e.g, anxiety, depression) (Brenner, Vanderploeg, & Terrior, 2009; Yurgil et al., 2014) frequently emerge post-injury. Collectively, these enduring neurobehavioral symptoms contribute to considerable health care costs (Stroupe et al., 2013; Tanielian & Jaycox, 2008), and they play a fundamental role in frequently reported decreased quality of life (Schiehser et al., 2015), and increased rates of disability and unemployment observed

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in Veterans with history of head injury (Lippa et al., 2015). Importantly, although most individuals with mild TBI appear to fully recover within about one year post-injury, a subset of individuals—oftentimes referred to as the "miserable minority"—continue to experience long-term cognitive, psychiatric, and behavioral difficulties (Bigler, 2013a, b; Ruff, Camenzuli, & Mueller, 1996; Vanderploeg, Curtiss, Luis & Salazar, 2007). Unfortunately, the exact neuropathological mechanisms underlying the persistent sequelae of mild neurotrauma remain poorly understood since traditional neuroimaging techniques are generally insensitive to subtle neuropathological changes associated with mTBI, as conventional computed tomography (CT) and magnetic resonance imaging (MRI) scans have largely yielded normal results (Bigler, 2013a, 2013b; Brenner, 2011; McAllister, Sparling, Flashman, & Saykin, 2001).

The advent of more sophisticated neuroimaging technology, coupled with experimental animal modeling of TBI, has provided insight into pathophysiological mechanisms thought to underlie the negative health outcomes of Veterans with history of TBI. Biomechanical and animal models of TBI have demonstrated that direct, or primary injury, to neurons, glia, and vessels occurs during neurotrauma (Bigler & Maxwell, 2012; Blennow, Hardy, & Zetterberg, 2012; Chatelin et al., 2011; Kenney et al., 2015; LaPlaca et al., 2007; LaPlaca & Prado, 2010; Povlishock & Katz, 2005). Moreover, secondary pathophysiological cascades (i.e., neuroinflammation, edema, ischemia, Wallerian degeneration) exacerbate local injury sites and contribute to diffuse damage post-injury (Bigler & Maxwell, 2012; DeKosky, Blennow, Ikonomovic, & Gandy, 2013; Farkas & Povlishock, 2007; Johnson et al., 2013; Magnuson, Leonessa, & Ling, 2012). While more severe and heterogeneous pathology is observed in those with moderate or severe TBIs, the mechanisms underlying milder forms of neurotrauma remain less well understood, as precise modeling of mild TBI in experimental studies is challenging, and autopsy cases are exceedingly rare. Nevertheless, advanced MRI techniques (e.g., diffusion tensor imaging [DTI], arterial spin labeling [ASL]) have been utilized for in-vivo quantification of neurotrauma-related brain changes in Veterans (see Wilde et al., 2015 for review). However, while some studies find robust brain differences in Veterans with history of TBI relative to those with no history of head trauma (Mac Donald et al., 2011; Miller, Hayes, Lafleche, Salat, & Verfaellie, 2016; Petrie et al., 2014; Ponto et al., 2016), others fail to detect any alterations (Jorge et al., 2012; Levin et al., 2010).

The inconsistent nature of neuroimaging findings following TBI may be partially explained by the heterogeneous nature of injury, or alternatively, differences in sample characteristics, scanning parameters, and analytic techniques utilized. However, oftentimes unconsidered are (1) the dynamic relationship *between* brain variables of interest and (2) how *time* since injury may factor into brain changes. With respect to the former, studies of normal and pathological aging have consistently demonstrated that cerebral blood flow (CBF) plays a pivotal role in the maintenance of white matter (WM) tissue integrity (Burzynska et al., 2015; Chen, Rosas, & Salat, 2013; O'Sullivan et al., 2002; Salat, 2014; Steketee et al., 2016). Reduced CBF has been demonstrated to not only precede, but also directly contribute to negative WM micro- and macro-structural changes in older adults (Bernbaum et al., 2015; Brickman et al., 2009; Promjunyakul et al., 2015; Promjunyakul et al., 2016; ten Dam et al., 2007). Importantly, while both CBF and WM changes have been independently examined within TBI (Delano-Wood et al., 2015; Ponto et al., 2016; Vas et al., 2016), few studies have explored relationships *between* CBF and WM within this population. This is especially critical given CBF reductions could serve to exacerbate or contribute to any trauma-induced WM alterations well beyond the time of initial injury.

Unfortunately, the temporal course of the neuropathological consequences of TBI remains poorly understood (Greve & Zink, 2009; Povlishock & Katz, 2005). However, there is some evidence to suggest that both CBF and WM changes may differ depending upon phase of injury (Eierud et al., 2014; Niogi & Mukherjee, 2010). For example, though findings are mixed, fractional anisotropy (FA)—a marker of WM microstructural integrity derived from diffusion tensor imaging (DTI)—has been observed to be both elevated and decreased in various studies examining those with history of TBI in the acute phase of injury relative to those without history of head trauma (Croall et al., 2014; Ling et al., 2012; Mayer et al., 2012). On the other hand, decreased FA is more commonly reported in individuals with history of TBI in the chronic phase of injury (Miller et al., 2016; Wada, Asano, & Shinoda, 2012). Similarly, while studies vary in reporting either elevated or decreased CBF in the acute phase of injury (Doshi et al., 2015; Meier et al., 2015), decreased CBF is most commonly observed in those with history of TBI who are further removed for their initial injury when compared to controls (Fridley, Robertson, & Gopinath, 2015; Ge et al., 2009). While there is no general consensus as to what constitutes acute versus chronic phases of injury, most Veterans are many months to years removed from their initial injury (i.e., in the chronic phase) during assessment; although, there is considerable inter-subject variability in the time between injury and assessment within and across previous Veteran TBI studies (Delano-Wood et al., 2015; Jorge et al., 2012; Mac Donald et al., 2011; Miller et al., 2016). It is especially critical to take into account *time since injury* when relating CBF and WM integrity given there is some evidence—at least in the aging literature—to suggest that CBF changes may persist for some time before negative WM alterations are subsequently observed (Brickman et al., 2009; Promjunyakul et al., 2015; ten Dam et al., 2007).

Therefore, there is a critical need to not only consider how CBF and WM relate to one another, but also how this relationship may depend on time since a TBI event. The current study sought to examine the link between resting CBF of the cingulate cortex and WM integrity of the cingulum bundle—two largely overlapping neuroanatomical regions that are known to be especially vulnerable to TBI effects (Bigler, 2007; Wu et al., 2010). Clarification of such relationships may assist in providing insight into factors influencing disparate brain findings in the TBI literature and elucidate findings that show WM degeneration may evolve over time during the chronic phase of injury (Bendlin et al., 2008; Yeh et al., 2017). We hypothesize that (1) decreased CBF of the cingulate cortex will be associated with reduced WM integrity of the cingulum bundle and (2), that this association will become more pronounced the further removed individuals are from their injuries. Importantly, findings may assist in clarifying mechanisms underlying the poor long-term outcomes and increased risk for stroke and dementia observed in those with history of TBI (Barnes et al., 2014; Burke et al., 2013; Chen, Kang, & Lin, 2011; Lee et al., 2013).

2. Methods

Study participants were 37 Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn (OEF/OIF/OND) Veterans with history of mild or moderate TBI (mmTBI) recruited from outpatient clinics and posted recruitment flyers at the VA San Diego Hospital (VASDH) in La Jolla, California. The institutional review boards (IRBs) at the VA San Diego Healthcare System (VASDHS) and University of California, San Diego (UCSD) approved the study, and all study participants provided written and informed consent. Neuropsychological testing, TBI history interviews, and completion

of questionnaires occurred at the Veterans Medical Research Foundation building located on the VASDHS campus. All MRI scanning took place at the UCSD Center for Functional MRI.

2.1. TBI diagnostic procedure

The Department of Defense (DoD)/VA TBI Task Force criteria (2009) was used for diagnosis of mild or moderate TBI. The criteria for mild TBI include loss of consciousness (LOC) < 30 min, or alteration of consciousness (AOC) or post traumatic amnesia (PTA) < 24 h, while the criteria for moderate TBI were LOC > 30 min but < 24 h, or AOC > 24 h or PTA > 1 day but < 7 days. Per Clark et al. (2016) trained graduate level and post-baccalaureate research assistants completed TBI history interviews. Each study participant was assessed for both military (i.e., during enlistment in the US armed services) and non-military (i.e., prior to or after discharge from the military) related head injuries. All reported military-related injuries also include assessment of whether the mechanism of injury was blunt or blast-related. For any injury that met diagnostic criteria for mild or moderate TBI, the date of occurrence was recorded and time since the most recent TBI and date of evaluation was calculated for use in subsequent analyses.

The following exclusionary criteria were applied to the study sample overall: (1) severe TBI (loss of consciousness [LOC] ≥ 24 h, alteration of consciousness [AOC] > 24 h, or posttraumatic amnesia [PTA] ≥ 7 days); (2) prior history of major medical illnesses (e.g., myocardial infarction) or neurological conditions (e.g., multiple sclerosis, stroke); (3) current active suicidal and/or homicidal ideation, intent, or plan requiring crisis intervention; (4) current or past history of DSM-IV diagnosis of bipolar disorder, schizophrenia, other psychotic disorder, or cognitive disorder due to a general medical condition other than TBI; (5) DSM-IV diagnosis of current substance/alcohol dependence or abuse; (6) a positive toxicology screen as measured by the Rapid Response 10-drug Test Panel; and (7) any contraindications that prevented MRI scanning. Participants were included in the study if they were OEF/OIF/OND Veterans between the ages of 18–65, completed neuropsychological testing, and received both DTI and MPPCASL sequences.

2.2. Health status, combat exposure, & symptom rating scales

All study participants completed a background health questionnaire and height, weight, and blood pressure was collected at the time of their study visit. Exposure to wartime stressors and combat situations while on deployment was assessed using the Combat Exposure Scale (CES; Keane et al., 1989). Symptom rating scales that quantified current levels of posttraumatic stress (PTSD Checklist [PCL-M]; (Weathers et al., 1993), depression (Beck-Depression Inventory-II [BDI-II]; (Beck et al., 1996), and neurological symptoms (Neurobehavioral Symptom Inventory [NSI]; King et al., 2012) were also completed.

2.3. Neuroimaging data acquisition

All participants were scanned on a 3-Tesla General Electric MR750 whole-body MRI system with an eight-channel head coil. T1-weighted Anatomical Scan: A sagitally acquired high-resolution T1-weighted anatomical scan was collected using a 3D FSPGR sequence with the following parameters: FOV = 24 cm, 256 × 192 matrix, TR = 8.1 ms, TE = 3.192 ms, flip angle = 12°, TI = 550 ms, bandwidth = 31.25 kHz, and 172 1.2 mm slices.

DTI: DTI images were collected via dual spin echo EPI acquisition (Reese, Heid, Weisskoff, & Wedeen, 2003) with the following parameters: FOV = 24 cm, slice thickness = 3 mm, matrix size 128 × 128, in-plane resolution = 1.875 × 1.875 mm, TR = 8000 ms, TE = 88 ms, scan time: 12 min. Forty-three slices were acquired with 61 diffusion directions distributed on the surface of a sphere in conjunction with the electrostatic repulsion model (Jones, Horsfield, & Simmons, 1999) and a b value of 1500 s/mm^2. Collection also included one T2 weighted image with no diffusion (b = 0). Distortions due to a lack of magnetic field homogeneity were reduced via field map corrections.

Resting CBF: Time-of-flight angiogram was collected with a three-dimensional spoiled gradient echo sequence (FOV = 22 × 16.5 cm, slice thickness = 1 mm, 0.57 × 0.74 × 1 mm^3 resolution, TE = 2.7 ms, TR = 20 ms, flip angle 15°) in order to define the location for PCASL labeling. The imaging volume was prescribed to visualize arteries above the vertebral crossing, but below the basilar artery. Axial images were used to select the slice most perpendicular to bilateral vertebral and carotid arteries and this location was then set as the labeling plane in an effort to achieve optimal tagging efficiency for the whole brain PCASL scan.

Whole-brain ASL data was acquired during a resting state using an MPPCASL sequence. Importantly, MPPCASL mitigates the adverse effects of off-resonance fields and gradient imperfections on the inversion efficiency in traditional PCASL techniques (Jung, Wong, & Liu, 2010). In MPPCASL, the blood magnetization is modulated with multiple RF phase offsets, and the resulting signal is then fit to a model function to generate a CBF estimate. Parameters included 20 5 mm thick axial slices (1 mm gap), FOV = 24 cm, matrix 64 × 64, PCASL labeling duration = 2000 ms, post-labeling delay = 1600 ms, TR = 4200 ms, TE = minimum, volumes = 60, scan time = 5 min. To achieve CBF quantification in physiological units (mL/100 g-min), a 36-s cerebrospinal fluid (CSF) reference scan was obtained to estimate of the magnetization of CSF (TR = 4000 ms, TE = 3.3 ms, NEX = 9 90°excitation pulse which is turned off for first 8 repetitions to create PDW image contrast; Chalela et al., 2000). A 32-s minimum contrast scan was also acquired to adjust for coil inhomogeneities (TR = 2000 ms, TE = 11 ms, NEX = 2) during the CBF quantification step. Finally, a field map was acquired using a spoiled gradient echo sequence to correct for field inhomogeneities (TR = 500 ms, TE1 = 6.5 ms, TE2 = 8.5 ms, flip angle 45°, scan time = 1:10 min).

2.4. Neuroimaging data processing

2.4.1. T1-weighted anatomical image processing

T1 anatomical images were reconstructed and parcellated into regions of interest using FreeSurfer software (Dale, Fischl, & Sereno, 1999). Manual edits were performed to ensure proper region of interest (ROI) segmentation and gray and white matter differentiation.

2.4.2. DTI processing

DTI preprocessing utilized the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL) (Smith et al., 2004). Two field maps were utilized to unwarp EPI acquisitions, and all images were motion corrected and visually inspected occurred for quality control purposes. The FSL program *dtifit* was used for voxel-by-voxel calculation of the diffusion eigenvalues and to provide fractional anisotropy (FA), a directional measure of diffusion ranging from 0 (isotropic diffusion) and 1 (perfectly anisotropic diffusion) that is reflective of fiber integrity.

. 2.4.3 Tractography

TrackVis (Wang et al., 2007), using the fiber assignment by continuous tracking (FACT) algorithm, was used to generate the left and right cingulum bundle for each participant. First, a color-coded map, seen by loading the principle eigenvector image in FSL, was generated to display each voxel's main orientation of diffusion. This information, in conjunction with a non-diffusion weighted map, allowed the rater to place seed points for fiber tracking. An initial seed was placed inferior to the cingulum gyrus and superior to the corpus callosum in the coronal plane. Next, three additional seeds in the anterior portion, the middle, and the posterior portion were placed following the description of Concha, Gross, & Beaulieu (2005) to generate the entire cingulum bundle for each hemisphere. Finally, mean FA was extracted from the length of each generated tract for use in statistical analyses. See Fig. 1 for depiction of left cingulum bundle ROI used in analyses.

. 2.4.4 Resting CBF

Each subject's raw ASL data, field map, and anatomical data were uploaded for processing to the Cerebral Blood Flow Biomedical Informatics Research Network (CBFBIRN; cbfbirn.ucsd.edu;Shin, Ozyurt, & Liu, 2013) established at the UCSD Center for Functional Imaging. Field map and motion correction, skull-stripping, tissue segmentation, and conversion to absolute physiological units of CBF (mL/100 g tissue/min) were completed through CBFBIRN. Quantified CBF maps for each participant were downloaded to a local server where they were blurred to 4 mm full-width at half maximum. Next, T1 images and partial volume segmentations were registered to ASL space and down-sampled to the resolution of the ASL images using the Analysis of Functional NeuroImages (AFNI) package (Cox, 1996). A threshold was applied that removed values outside of the expected physiological range of CBF (< 10 or > 150; (Bangen et al., 2014), then whole brain gray matter CBF and regional gray matter CBF values from the Desikan et al. (2006) atlas were extracted. Mean perfusion of the cingulate cortex was calculated as the average of the following gray matter ROIs for each hemisphere with each region's contribution to the average weighted by the volume of the region: rostral and caudal anterior cingulate, posterior cingulate and isthmus of the cingulate. See Fig. 1 for a lateralized depiction of the left cingulate cortex utilized in this study.

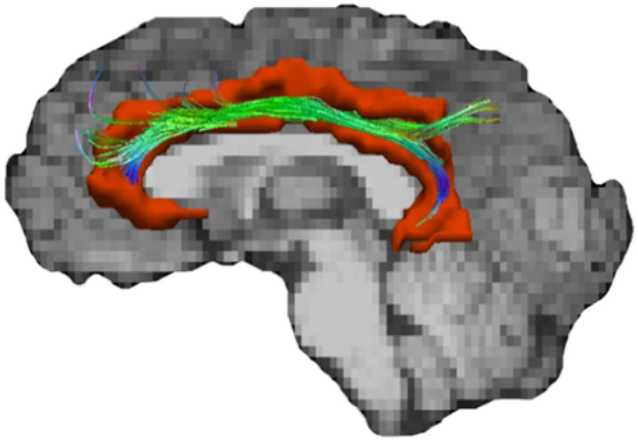

Fig. 1. Lateralized depiction of the regions of interested utilized in the current study. The left cingulum bundle fiber track is superimposed on the left cingulate cortex (red). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.5. Statistical analyses

Multiple linear regressions were performed to determine (1) whether there was an association between CBF of the cingulate cortex and WM microstructural integrity of the cingulum bundle and (2) whether this association was modified by time since injury. A median split for time since injury was conducted to dichotomize TBI participants into two groups. Chi-squared analyses were utilized to compare the groups in terms of categorical variables and analysis of variance (ANOVA) was used for continuous variables. All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 21 (SPSS IBM, New York, USA).

3. Results

Participant demographics, TBI characteristics, and symptom rating scales for the sample are presented in Table 1. Participants were predominantly young (*Mean age* = 33.38 years) male (89%) Veterans who were blast-exposed (49%) and experienced moderate levels of combat exposure (*Mean total score of* 16.23 on Combat Exposure Scale) while on deployment. With respect to TBI injury characteristics, a greater proportion of Veterans experienced loss (65%) versus alteration of consciousness during their most significant TBI, these injuries were predominantly mild in severity (81%), and on average many months had passed since their most recent head injury (*Mean time* = 69.05). Symptom rating scales revealed participants endorsed sub-threshold levels of posttraumatic stress symptoms (*Mean PCL-M total score* = 47.57) and depressive symptoms were moderate in severity (*Mean BDI-II total score* = 21.14).

3.1. Resting CBF and WM associations

A set of multiple linear regressions were performed for each hemisphere in an effort to determine if there was an association between resting CBF of the cingulate cortex and white matter mi-

Table 1
Participant characteristics.

	Mean (SD)
Age	33.38 (6.05)
Education	14.54 (1.56)
WRAT-4 reading standard score	102.63 (12.45)
Gender (% Male)	89.2%
Ethnicity	
Caucasian	35.1%
African-American	8.1%
Hispanic	37.8%
Asian	16.2%
Native American	2.7%
Combat exposure scale	16.23 (12.06)
PCL-M total score	47.57 (18.36)
BDI-II total score	21.14 (12.52)
NSI total score	37.11 (18.96)
Months since injury (months)	69.05 (38.09), median = 62.00, range = 148
Total # of TBIs	2.84 (1.48)
TBI severity (% mild)	81%
% most significant TBI with LOC	65%
Blast-exposed (% yes)	49%
Pulse pressure (n = 36)	45.65 (8.28)
Height (in.)	67.93 (3.30)
Weight (lbs)	193.03 (45.58)
Current smoker (% yes)	16%
APOE-ε4 genotype (n = 35; % yes)	31%

WRAT-4 = wide range achievement test-4th edition; PCL-M = posttraumatic stress disorder checklist; BDI-II = Beck depression inventory 2nd edition; NSI = neurobehavioral symptom inventory; APOE-ε4 = apolipoprotein-ε4 carrier.

crostructural integrity of the cingulum bundle. In each model age, sex, PCL-M total score, and resting CBF of the cingulate cortex were entered as predictors. Results revealed that neither the left (β = 0.08, $p = 0.67$) or right (β = 0.03, $p = 0.88$) cingulate cortex CBF predicted left or right cingulum bundle FA, respectively.

3.2. Resting CBF, time since injury, and WM integrity

A second set of multiple linear regressions were performed for each hemisphere to determine whether time since injury moderated the association between resting CBF of the cingulate cortex and cingulum bundle FA. In the first model, FA of the left cingulum bundle was entered as the dependent variable; age, sex, PCL-M total score, resting CBF of the left cingulate cortex, time since injury, and an interaction term (resting CBF of left cingulate cortex X time since injury) were entered as independent variables. As shown in Table 2, results revealed there was a significant resting CBF of the left cingulate cortex × time since injury interaction on FA of the left cingulum bundle (β = 7.05, $t = 3.99$, $p < 0.001$). A median split for time since injury was conducted for further inspection of this relationship (see Fig. 2). Examination of simple main effects revealed that there was a significant positive correlation between resting CBF of left cingulate cortex and left cingulum bundle FA ($r = 0.48$, $p = 0.04$, n = 19) in Veterans furthest removed from their time since injury (≥ 62 months). However, for Veterans whose injuries were more recent (< 62 months), there was no significant association between resting CBF of the left cingulate cortex and left cingulum bundle FA ($r = -0.19$, $p = 0.46$, n = 18). Results did not differ when total number of TBIs was included as a covariate in a secondary set of analyses and total number of TBIs (β = 0.13, $t = 0.67$, $p = 0.51$) was not a significant predictor of FA of the left cingulum bundle in the model. When this set of analyses was performed for the right hemisphere, there was no significant resting CBF of right cingulate cortex X time since injury interaction on FA of the right cingulum bundle (β = − 0.99, $t = 0.44$, $p = 0.66$).

Table 2
Multiple linear regression models for left cingulum bundle FA.

	R^2	F	Standardized β	t	p
	0.445	4.01			0.005
Age			− 0.304	− 1.90	0.07
Gender			− 0.359	− 2.55	0.02
PCL-M total score			− 0.007	− 0.052	0.96
Time since injury			− 7.02	− 3.97	0.000
CBF of left cingulate cortex			− 1.19	− 3.37	0.002
CBF × time since injury			7.05	3.99	0.000

3.3. Group comparisons for phase of injury

In an effort to further understand the significant association between resting CBF of the left cingulate cortex and FA of the left cingulum bundle, participant demographics, TBI injury characteristics, and symptom rating scales were compared for participants who were closer versus further removed from their time since injury (see Table 3). Results revealed the groups were comparable on all comparisons except for time since injury. Although not statistically significant, there were a greater proportion of individuals in those further removed from their TBI whose injuries were moderate (rather than mild) in severity. However, when a secondary set of analyses where TBI injury severity was included in the original regression model results remained the same and TBI injury severity was not a significant predictor of FA of the left cingulum bundle (β = 0.04, $t = 0.25$, $p = 0.80$). Moreover, sensitivity analyses revealed that when those with moderate TBIs (n = 7) were excluded from this analysis entirely, the significant interaction of resting CBF x time since injury on FA of the left cingulum bundle remained (β = 6.84, $t = 3.58$, $p = 0.002$).

4. Discussion

The current study explored (1) the association between neuroimaging biomarkers of CBF and WM, and (2) the potential influence of time since injury on this relationship in Veterans with history of mmTBI. Results showed an interaction between time since injury and CBF of the left cingulate cortex on WM integrity of the left cingulum bundle. Specifically, in Veterans who were furthest removed from their time since injury, decreased CBF was significantly associated with reduced FA of the cingulum region. These findings provide preliminary evidence for a dynamic association between CBF and WM that may also play a pivotal role in increased risk for negative health outcomes (e.g. stroke, dementia) commonly observed in individuals with history of TBI. It is possible that this dynamic association observed between CBF and WM may partially explain the mixed findings in the neuroimaging literature, particularly since the vast majority of existing studies have focused on a single neuroimaging modality.

While our understanding of the pathophysiological consequences of TBI has improved, the time course of brain changes post-injury remains less well understood. Recent evidence suggests that TBI-re-

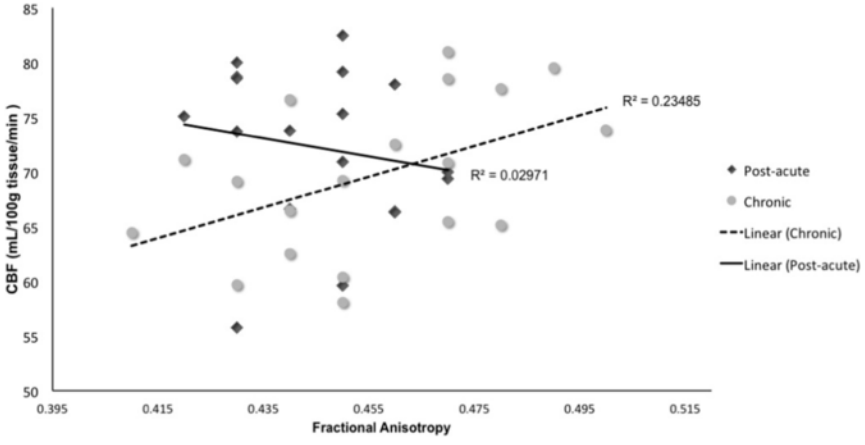

Fig. 2. Cerebral blood flow (CBF) of left cingulate cortex × time since injury for left cingulum bundle fractional anisotropy

Table 3
Group comparisons for phase of injury.

	Post-acute group mean (sd) n = 18	Chronic group mean (sd) n = 19	*F* or χ^2	*p*
Age	33.11 (1.71)	33.63 (4.79)	0.07	0.80
Gender (% male)^	83.3%	94.7%	1.29	0.26
Ethnicity^			2.74	0.34
Caucasian	33.8%	36.8%		
African-American	5.6%	10.5%		
Hispanic	33.3%	42.1%		
Asian	22.2%	10.5%		
Native American	5.6%	0%		
Combat exposure scale	13.96 (11.97)	18.38 (12.09)	1.25	0.27
PCL-M total score	51.28 (16.92)	44.07 (19.41)	1.44	0.24
BDI-II total score	24.44 (12.11)	18.01 (12.39)	2.55	0.12
NSI total score	42.30 (18.47)	32.11 (18.51)	2.86	0.10
Months since injury (months)	39.28 (15.97)	97.26 (30.57)	51.39	< 0.001
Total # of TBIs	2.89 (1.56)	2.79 (1.43)	0.04	0.84
TBI Severity (% mild)^	88.9%	73.7%	1.44	0.23
% most significant TBI with LOC	55.6%	73.7%	1.34	0.25
Blast-exposed (% yes)	44.4%	52.6%	0.25	0.62
Pulse pressure (n = 18, n = 18)	46.22 (7.34)	45.08 (9.31)	0.17	0.69
Height	67.75 (3.93)	68.11 (2.70)	0.75	0.75
Weight	191.78 (48.92)	194.28 (43.37)	0.87	0.87
Current smoker (% yes)^	17%	16%	0.23	0.24
APOE-ε4 genotype (% yes)	35%	28%	0.63	0.63

^Likelihood ratio; PCL-M = posttraumatic stress disorder checklist; BDI-II = Beck depression inventory 2nd edition; NSI = neurobehavioral symptom inventory; APOE-ε4 = apolipoprotein-ε4 carrier.

lated brain changes are not static, but may continue to evolve many months to years following the initial insult. For example, Venkatesan et al. (2015) utilized resting state functional MRI (rs-fMRI) to explore the trajectory of connectivity patterns between the acute and chronic phase of injury in individuals with history of moderate-to-severe TBI. Results revealed that, relative to controls, the TBI group not only demonstrated altered connectivity patterns, but that these differences *intensified* from the acute to chronic phase of injury. In the present study, CBF and WM associations were only evident in those furthest removed from injury. It may be that this association is a manifestation of pathological processes that are characteristic of more chronic injury phases. Alternatively, as the aging literature has shown, CBF reductions may need to persist for some time before WM alterations arise (ten Dam et al., 2007; Brickman et al., 2009; Promjunyakul et al., 2015). Importantly, we cannot ascribe our results to exact causal or directional etiologies given the cross-sectional nature of this study and future studies are needed to further elucidate the time course of these dynamic relationships. Moreover, given this sample reflects mild TBI, there is also a critical need to clarify to what extent the observed findings may apply to samples comprising primarily moderate or severe injuries.

Our finding of an association between CBF and WM in those most remote from their injury aligns well with existing literature demonstrating a pronounced co-variation between WM integrity and vascular function in both healthy and pathological aging samples (Burzynska et al., 2015; Chen et al., 2013; O′Sullivan et al., 2002; Steketee et al., 2016). Within the context of TBI, CBF may play an important role in identifying those at risk for secondary WM changes following injury. For example, in an emergency room sample with mild TBI, decreased CBF at baseline assessment (within hours of injury) was tightly linked with reduced WM integrity at follow-up (on average 5 months post-injury; Metting, Cerliani, Rodiger, & van der Naalt, 2013). The establishment of a relationship between CBF and WM within the context of head injury is critical, as maintenance of vascular health may be a critical point of intervention in the prevention of additional brain damage in those with history of TBI. Indeed, population-based studies have demonstrated that history of TBI is associated with increased risk for stroke (Burke et al., 2013; Chen et al., 2011), which reportedly persists for many years following the initial trauma (Chen et al., 2011).

Capturing brain changes in mild TBI is difficult, and it is possible that other neuroimaging metrics not directly examined here (e.g., cortical thickness) may also influence the CBF-WM associations observed in the current study. For example, a study by Duering et al. (2012) used longitudinal MRI methods to study how subcortical infarcts influence cortical morphology post-stroke. They found that damage to subcortical white matter initiated a secondary neurodegenerative process within cortical gray matter. Moreover, structural changes in the form of cerebral atrophy have also been linked to CBF reductions in other clinical populations (Appelman et al., 2008; Wirth et al., 2016). Unfortunately, work teasing apart primary and secondary injury processes within the context of TBI is still in its infancy, and prospective and longitudinal study designs with well-characterized samples are needed to tease apart how brain variables may interact with one another, especially over time, and ultimately influence behavioral outcomes.

Our secondary analyses revealed that the observed CBF and WM relationship in those furthest removed from their injury was not driven by fundamental differences in psychological, post-concussive, health, or injury characteristics relative to those whom were closer in time to their injury. Interestingly, both CBF and WM alterations have also been observed in those with elevated vascular risk in mid-to-late life (Beason-Held et al., 2012; Bangen et al., 2014; Maillard et al., 2015; Wang et al., 2007); however, it is unclear to what extent TBI may increase the prevalence of vascular risk factors and whether individuals with elevated vascular risk are uniquely vulnerable to negative brain changes post-TBI. Future studies that include more comprehensive assessment of vascular risk are needed to understand how history of TBI and vascular risk factors may interact to affect the brain, cognition, and functional outcomes post-injury.

To our knowledge, this is the first study to investigate both ASL and DTI in the context of military TBI. However, there are several limitations that warrant discussion. Given the cross-sectional nature of this study, we cannot determine causal relationships between reduced CBF and reduced FA. Secondly, we were unable to explore whether these associations differ across mechanism of injury (i.e., blast versus blunt) or with blast-exposure given sample size restrictions. As is common with military studies of TBI, diagnosis of mild or moderate TBI was based entirely upon retrospective self-report of injuries and may therefore be subject to recall bias. We chose to examine CBF and WM of two closely linked neuroanatomical regions that are known to be vulnerable to the effects of neurotrauma; however, future studies will need to examine these effects across the brain and with other DTI metrics (i.e., axial and radial diffusivity) to further elucidate CBF and WM relationships. Replication with larger sample sizes and longitudinal designs are also needed to provide more insight into the complex associations between WM integrity and CBF at different stages post-TBI.

5. Conclusion

Taken together, results indicate that, even after adjusting for psychiatric symptomatology, an association between CBF and WM exists in those with history of mmTBI. Although the exact nature and

timeline of brain changes post-TBI is unclear, CBF and WM alterations may play a pivotal role in the increased risk for negative health outcomes (e.g. stroke, dementia) that are observed in individuals with history of TBI. Currently, there is an ever-pressing need to consider how brain changes may differ with time and what might mediate or moderate these changes following injury. These findings contribute to our understanding of the possible dynamic relationship between CBF and white matter integrity, and they enhance our understanding of potential pathophysiological mechanisms that exist in the post-acute phase of injury.

Compliance with ethical standards & disclosures

All procedures involved in this study were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975. Informed consent was obtained from all patients included in the study. Alexandra Clark, Katherine Bangen, Lisa Delano-Wood, Scott Sorg, Dawn Schiehser, Nicole Evangelista, and Thomas Liu declare no conflicts of interest.

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